Archive of 2002 Online Issues:

2002

January	February	March
January 2002; 180 (1): 1 - 92	February 2002; 180 (2): 97 - 190	March 2002; 180 (3): 193 - 290
April	**May**	**June**
April 2002; 180 (4): 293 - 386	May 2002; 180 (5): 389 - 472	June 2002; 180 (6): 475 - 557
July	**August**	**September**
July 2002; 181 (1): 1 - 86	August 2002; 181 (2): 91 - 178	43; 1 - 106 European First-Episode Schizophrenia Network: E September 2002; 181 (3): 181 - 268
October	**November**	**December**
October 2002; 181 (4): 0 - 0	November 2002; 181 (5): 363 - 454	December 2002; 181 (6): 457 - 548

© 2010 The Royal College of Psychiatrists.

Efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants: a meta-analysis*

DAVID SMITH, CARRIE DEMPSTER, JULIE GLANVILLE, NICK FREEMANTLE and IAN ANDERSON

Background In individual studies and limited meta-analyses venlafaxine has been reported to be more effective than comparator antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs).

Aims To perform a systematic review of all such studies.

Method We conducted a systematic review of double-blind, randomised trials comparing venlafaxine with alternative antidepressants in the treatment of depression. The primary outcome was the difference in final depression rating scale value, expressed as a standardised effect size. Secondary outcomes were response rate, remission rate and tolerability.

Results A total of 32 randomised trials were included. Venlafaxine was more effective than other antidepressants (standardised effect size was −0.14, 95% CI −0.07 to −0.22). A similar significant advantage was found against SSRIs (20 studies) but not tricyclic antidepressants (7 studies).

Conclusions Venlafaxine has greater efficacy than SSRIs although there is uncertainty in comparison with other antidepressants. Further studies are required to determine the clinical importance of this finding.

Declaration of interest The study was funded by Wyeth Laboratories. D.S. has received funding on another study from Wyeth Laboratories and N.F. and I.A. have received speaker's fees and honoraria in connection with this work.

Depressive disorders are the second most important cause of disability in developed countries (Murray & Lopez, 1997) but a substantial minority of depressed patients fail to respond to antidepressant treatment (Anderson *et al*, 2000). Although newer antidepressants have tolerability and safety benefits over older tricyclic antidepressants (TCAs), similar efficacy generally is reported (Edwards, 1992; Gross & Huber, 1999; Anderson, 2000; Geddes *et al*, 2001). It is potentially of great clinical importance if an antidepressant were to be more effective than comparators, and understanding why may shed light on how antidepressants work. It has been proposed (Nelson *et al*, 1991; Seth *et al*, 1992; Heninger *et al*, 1996) that antidepressants with a dual action of inhibiting the re-uptake of both noradrenalin and serotonin (5-hydroxytryptamine, 5-HT) may be more effective than drugs acting on a single monoamine (e.g. selective serotonin re-uptake inhibitors, SSRIs). Venlafaxine is the first drug to be marketed that inhibits both noradrenalin and 5-HT reuptake without actions at other receptors (Holliday & Benfield, 1995). We present a systematic review investigating the relative efficacy and tolerability of venlafaxine compared with other antidepressants.

METHOD

Relevant trials were identified from our existing database (Eccles *et al*, 2000) and from systematic searches of electronic databases. The search terms were VENLAFAXINE, EFEXOR or EFFEXOR. Databases searched included Medline, Embase, Biosis, PsychLit, National Research Register, Healthstar, SIGLE, Cochrane Database of Systematic Reviews, DARE, Cochrane Controlled Trials Register and Current Controlled Trials. A total of 2349 trials were identified from our electronic search strategy. We carried out a manual search of reference lists of included studies and requested unpublished data from authors and study sponsors.

Inclusion criteria

Trials were included if they were double-blind, randomised studies comparing venlafaxine with an alternative antidepressant for the treatment of depression. The definition of depression was intentionally broad and included explicit clinical or research criteria for major depression (such as DSM–IV; American Psychiatric Association, 1994) or if the clinician considered the patient to be depressed and eligible for antidepressant treatment. Two of the researchers (D.S. and C.D.) made an independent assessment of each potentially eligible study and disagreements were resolved through discussion within the team.

Data abstraction

Design characteristics and quality assessment

We abstracted data on the inclusion and exclusion criteria for each study, the dose and regimen of venlafaxine and alternative antidepressants, the adequacy of randomisation and concealment of allocation (as reported in the paper), number of patients randomised, loss to follow-up, form of analysis (completer analysis or last observation carried forward), relevant clinical outcomes reported, age and gender of participants and length of follow-up. When specific variables were not reported within a given trial, the authors of the paper were contacted to obtain the missing data. If this was unsuccessful, we contacted the sponsors. Data were abstracted on all available patients randomised in the trials and patients were analysed on the basis of initial random allocation to treatment group (intention to treat) whenever possible.

Clinical outcomes

The primary outcome was the mean depression severity measure assessed by the final

*The Editor, Greg Wilkinson, is in receipt of a consultancy fee from Neurolink (sponsored by Wyeth) so took no part in, and was kept blind to, the assessment of this paper. After enquiries by Professor Wilkinson, neither the Editorial Board member who acted as Editor in respect of this paper, nor those assessors who took part in the peer-review process, declared any interest relevant to the publication of this paper.

Table 1 Description of included trials[1]

Drug class	Comparator	Trial	Citation	No. of studies	No. of patients	Venlafaxine dose	Mean age	Female (%)	Method	Setting
TCA				9	1508	131[5]	50	68[5]		
	Amitriptyline	Gentil *et al*, 2000	23	1	116	103	39	81	LOCF	Out-patient
	Clomipramine	Smeraldi *et al*, 1998	24	2	113	83	72	73	LOCF	Out-patient
		Samuelian & Hackett, 1998	25		102	105	47	62	LOCF	Out-patient
	Dothiepin (dosulepin)	Mahapatra & Hackett, 1997	26	2	92	100	74	70	LOCF	Out-patient
		Stanley *et al*, 1998	14		86	75	NA	NA	Completers	Out-patient
	Imipramine	Shrivastava *et al*, 1994	27	4	381	165	43	54	LOCF	Out-patient
		Benkert *et al*, 1996	28		167	233	47	68	LOCF	In-patient
		Lecrubier *et al*, 1997	29		153	111	40	69	LOCF	Out-patient
		Schweizer *et al*, 1994	30		146	182	42	66	LOCF	Out-patient
SSRI				20	3989	150[5]	47	67[5]		
	Fluoxetine	Costa & Silva, 1998	31	13	382	91	40	79	LOCF	Out-patient
		Tylee *et al*, 1997	15		341	75	45	71	Completers	Out-patient
		Dierick *et al*, 1996	32		314	111	44	65	LOCF	Out-patient
		Rudolph *et al*, 1998	33		308	300			Not clear	Out-patient
		Silverstone & Ravindran, 1999	34		249	141	42	60	Completers	Out-patient
		Schatzberg & Cantillon, 2000	35		204	150	71	50	LOCF	Out-patient
		Rudolph & Feiger, 1999	36		203	175	40	70	LOCF	Out-patient
		Unpublished data[2]	37		196	150	NA	NA	LOCF	Out-patient
		Unpublished data[3]	38		156	150	NA	NA	LOCF	Out-patient
		Geerts *et al*, 1999	39		146	102	43	68	LOCF	Out-patient
		Tzanakaki *et al*, 2000	40		109	225	48	79	LOCF	In-patient
		Alves *et al*, 1999	41		87	113	NA	NA	LOCF	Out-patient
		Clerc *et al*, 1994	42		68	200	51	68	LOCF	In-patient
	Fluvoxamine	Unpublished data[4]	43	2	92	150	NA	NA	LOCF	Out-patient
		Zanardi *et al*, 2000	44		28	225	51	64	LOCF	In-patient
	Paroxetine	McPartlin *et al*, 1998	45	4	361	75	45	68	LOCF	Out-patient
		Salinas, 1997	46		246	113	47	63	LOCF	Out-patient
		Poirier & Boyer, 1999	47		123	269	43	72	LOCF	Out-patient
		Ballus *et al*, 2000	48		84	113	NA	NA	LOCF	Out-patient
	Sertraline	Mehtonen *et al*, 2000	49	1	147	114	43	66	LOCF	Out-patient
Other				3	418	166[5]	53	64[5]		
	Mirtazapine	Guelfi, 1999	50	1	157	255	45	64	LOCF	In-patient
	Trazodone	Cunningham *et al*, 1994	51	2	149	160	41	55	LOCF	Out-patient
	Trazodone	Smeraldi *et al*, 1998	24		112	83	72	72	LOCF	Out-patient
Total				32	5562	147[5]	48	67[5]		

TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; LOCF, last observation carried forward.

1. Multiple comparisons were made in a number of trials. As a quality criterion, and a rule of thumb, we cite the total number of patients in the trials, rather than the comparisons included, because there is good empirical evidence that the quality of studies is affected directly by the overall size.
2. Unpublished data: Nemeroff, C & Amchin, J. (1998) Placebo-controlled trial of the efficacy and tolerability of venlafaxine and fluoxetine in outpatients with major depression (abstract P.1.066). 11th European Congress of Neuropsychopharmacology, Paris, France.
3. Unpublished data: Kornaat, H. (1998) Randomised, double-blind comparison of venlafaxine and fluoxetine for moderately depressed outpatients (abstract PM02021). XXIth Congress of the Collegium Internationale Neuro-Psychopharmacologicum, Glasgow, UK.
4. Unpublished data: Hackett D., Salinas, E. & Desmet, A. (1998) Efficacy and safety of venlafaxine vs. fluvoxamine in outpatients with major depression (abstract P.1.210). 11th European Congress of Neuropsychopharmacology, Paris, France.
5. Weighted mean.

(end of trial) Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960), the Montgomery and Åsberg Depression Rating Scale (Montgomery & Åsberg, 1979) or the Clinical Global Impression (Guy, 1976), with preference given in that order if more than one scale was reported. Secondary outcome variables were response rate (typically 50% or greater drop in depression rating scale from baseline) and remission rate (depression rating scale below a certain score, e.g. HRSD <8). Data on tolerability were abstracted by collecting 'all cause' withdrawals from each treatment group and also the attributed reason for withdrawal from therapy (lack of efficacy and adverse effects).

Statistical analysis

The primary efficacy outcome was the pooled standardised difference in mean treatment effect. For this measure, standardised effect sizes (difference in final rating scale means divided by the within-study standard deviation) were estimated from the efficacy data for each treatment group. Where an estimate of study variance was not available, this was imputed by taking the average for the studies using the same outcome measure. Secondary binary outcomes of response and remission, as well as tolerability data, were calculated as the odds ratio and absolute risk difference.

A simulation method was used to estimate pooled treatment effects using Gibbs sampling in BUGS software (Smith *et al*, 1995; Freemantle *et al*, 1999). This method is analogous to standard methods but does not require large sample assumptions, making it superior in meta-analysis where these assumptions frequently are not met. It has the additional advantage that the predictive value of different factors, such as patient severity or dose, may be examined using meta-regression approaches (Freemantle *et al*, 1999). Absolute risk differences were calculated using standard methods (DerSimonian & Laird, 1986) and interpreted as 'number needed to treat' (NNT). Negative NNTs are often described as 'number needed to harm'.

Fixed effects approaches to meta-analysis assume that each trial contributes an estimate of a constant population effect for a treatment, whereas random effects approaches assume that there is no single population effect but a *distribution* (range)

Table 2 Effect size analysis

Class	Comparator	Effect size	95% CI	Study
TCA	Amitriptyline	0.26	−0.10 to 0.63	Gentil *et al*, 2000
	Pooled amitriptyline	0.26	−0.10 to 0.63	
	Clomipramine	0.05	−0.32 to 0.42	Smeraldi *et al*, 1998
	Clomipramine	−0.11	−0.51 to 0.28	Samuelian & Hackett, 1998
	Pooled clomipramine	−0.03	−0.29 to 0.24	
	Dothiepin	−0.02	−0.44 to 0.4	Mahapatra & Hackett, 1997
	Dothiepin	−0.18	−0.71 to 0.36	Stanley *et al*, 1998
	Pooled dothiepin	−0.08	−0.40 to 0.24	
	Imipramine	−0.4	−0.64 to −0.16	Shrivastava *et al*, 1994
	Imipramine	−0.32	−0.65 to 0.02	Schweizer *et al*, 1994
	Pooled imipramine	−0.38	−0.57 to −0.19	
	Pooled TCA	−0.13	−0.33 to 0.09	
SSRI	Fluoxetine	−0.02	−0.22 to 0.19	Costa & Silva, 1998
	Fluoxetine	0.18	−0.07 to 0.43	Tylee *et al*, 1997
	Fluoxetine	−0.18	−0.40 to 0.04	Dierick *et al*, 1996
	Fluoxetine	−0.14	−0.37 to 0.09	Rudolph *et al*, 1998
	Fluoxetine	−0.12	−0.37 to 0.14	Silverstone & Ravindran, 1999
	Fluoxetine	−0.48	−0.76 to −0.2	Schatzberg & Cantillon, 2000
	Fluoxetine	−0.21	−0.49 to 0.07	Rudolph & Feiger, 1999
	Fluoxetine	−0.22	−0.50 to 0.06	Unpublished data[1]
	Fluoxetine	0.02	−0.30 to 0.35	Unpublished data[2]
	Fluoxetine	−0.5	−0.85 to −0.15	Geerts *et al*, 1999
	Fluoxetine	−0.08	−0.46 to 0.3	Tzanakaki *et al*, 2000
	Fluoxetine	−0.34	−0.77 to 0.1	Alves *et al*, 1999
	Fluoxetine	−0.58	−1.06 to −0.09	Clerc *et al*, 1994
	Pooled fluoxetine	−0.14	−0.22 to −0.06	
	Fluvoxamine	0.56	−0.23 to 1.34	Zanardi *et al*, 2000
	Pooled fluvoxamine	0.56	−0.23 to 1.34	
	Paroxetine	−0.1	−0.31 to 0.12	McPartlin *et al*, 1998
	Paroxetine	−0.46	−0.73 to −0.19	Salinas, 1997
	Paroxetine	−0.07	−0.42 to 0.29	Poirier & Boyer, 1999
	Paroxetine	−0.07	−0.50 to 0.37	Ballus *et al*, 2000
	Pooled paroxetine	−0.19	−0.34 to −0.05	
	Sertraline	−0.31	−0.67 to 0.06	Mehtonen *et al*, 2000
	Pooled sertraline	−0.31	−0.67 to 0.06	
	Pooled SSRI	−0.17	−0.27 to −0.08	
Other	Mirtazapine	0.23	0.55 to −0.09	Guelfi, 1999
	Pooled mirtazapine	0.23	0.55 to −0.09	
	Trazodone	−0.11	−0.44 to 0.23	Cunningham *et al*, 1994
	Trazodone	−0.37	−0.74 to 0.01	Smeraldi *et al*, 1998
	Pooled trazodone	−0.23	−0.47 to 0.02	
	Pooled 'other drug'	−0.09	−0.42 to 0.23	
Overall pooled		−0.14	−0.22 to −0.07	

TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor.
1. Unpublished data: Nemeroff, C & Amchin, J. (1998) Placebo-controlled trial of the efficacy and tolerability of venlafaxine and fluoxetine in outpatients with major depression (abstract P1.066). IIth European Congress of Neuropsychopharmacology, Paris, France.
2. Unpublished data: Kornaat, H. (1998) Randomised, double-blind comparison of venlafaxine and fluoxetine for moderately depressed outpatients (abstract PM02021). XXIth Congress of the Collegium Internationale Neuro-Psychopharmacologicum, Glasgow, UK.

of effects. Random effects models were used where venlafaxine was compared with a variety of agents (e.g. in comparison with SSRIs) but fixed effects models were used where venlafaxine was compared with individual agents.

Meta-regression was used to examine the predictive value of potentially important explanatory factors on the primary efficacy outcome measure (Freemantle *et al*, 1999). This hierarchical approach to data modelling enables examination of the effect of trial characteristics while preserving the structure of individual trials. The factors that we identified *a priori* were: size of trial; in-patient *v.* out-patient status; design criteria (last observation carried forward *v.* completer analysis). The analysis on size of trial is a particularly helpful method of identifying potential publication bias and is analogous to using a funnel plot. Other factors also investigated were age and gender, comparator drug class, length of follow-up, rating scale used (e.g. HRSD or Montgomery and Åsberg Depression Rating Scale), dose of venlafaxine and if the variance was imputed.

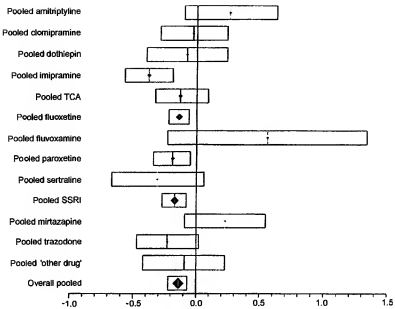

Fig. 1 Plot of pooled efficacy of venlafaxine compared with other antidepressants. The bars show the effect size (difference in final rating scale score divided by pooled final standard deviation) and the 95% CI. Results falling to the left of the line of no effect (zero) indicate an advantage to venlafaxine.

RESULTS

Included trials

A total of 32 studies met the inclusion criteria (Table 1), with comparisons of venlafaxine with TCAs (clomipramine, imipramine, dothiepin (dosulepin) and amitriptyline), SSRIs (fluoxetine, fluvoxamine, paroxetine and sertraline) and other drugs (trazodone and mirtazapine). There were 5562 patients in total[1]: 3844 in the twenty trials comparing venlafaxine with SSRIs (SSRI n=1857); 1356 in the nine trials comparing venlafaxine with TCAs (TCA n=579); and 418 in the three trials comparing venlafaxine with other drugs (other n=212). The average trial size was 179 patients (range 28–382). The average length of follow-up was 10 weeks (range 4–48). Most trials used the last observation carried forward for the primary analysis (see Table 1). For three of the trials, we imputed the measure of variance because the data were not available and could not be obtained from the authors or sponsors. None of the trials indicated whether concealment of allocation was conducted appropriately.

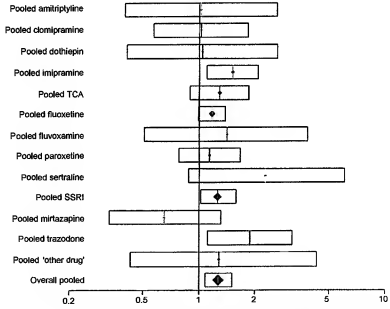

Fig. 2 Plot of pooled response rate to venlafaxine compared with other antidepressants. The bars show the odds ratio and the 95% CI. Results falling to the right of the line of no effect (1) indicate an advantage to venlafaxine.

1. Multiple comparisons were made in a number of trials. As a quality criterion, and a rule of thumb, we cite the total number of patients in the trials, rather than the comparisons included, because there is good empirical evidence that the quality of studies is affected directly by the overall size.

Primary outcome

There were 29 comparisons in the effect size analysis of clinical efficacy (Table 2). The overall effect size estimate was −0.14

(95% CI −0.22 to −0.07) in favour of venlafaxine. The size of effect (given a pooled standard deviation of 8.3) is equivalent to the final HRSD score, being about 1.2 points lower on venlafaxine. For the SSRIs, the effect size estimate was −0.17 (95% CI −0.27 to −0.08). Effect sizes for the TCAs and the 'other drug' categories were similar but not significantly different from venlafaxine (Table 2, Fig. 1).

The results appeared consistent across the SSRIs but there were differences between the TCA studies, notably imipramine: the effect size was −0.38 (95% CI −0.57 to −0.19), favouring venlafaxine, whereas there was no benefit in studies against other TCAs (Table 2, Fig. 1).

Response rates

Table 3 shows the estimated response rates. The overall odds ratio for response was 1.27 (95% CI 1.07–1.52). The risk difference was 0.05 (95% CI 0.02–0.09), with an NNT of 19 (95% CI 11–63). The pooled results for different drug classes were similar to this overall effect (Fig. 2).

Remission rates

Table 4 and Fig. 3 display the pooled remission results. The overall odds ratio for remission rate was 1.36 (95% CI 1.14–1.61), favouring venlafaxine. The overall risk difference was 0.07 (95% CI 0.03–0.11), giving an NNT of 14 (95% CI 9–29).

Remission rates were measured in only 18 of the trials and, of these, 16 used an SSRI agent as the comparator. The result for the pooled SSRI comparison was similar to the overall effect.

None of the factors that were hypothesised to influence the estimate of primary outcome were significantly predictive of greater efficacy in meta-regression analyses (analysis not shown).

Meta-regression analysis and visual inspection of funnel plots provided no evidence of publication bias, although did not exclude the possibility of the existence of such bias.

Treatment discontinuation

Table 5 shows an analysis of drop-outs by reason and comparator drug class. The overall risk difference of −0.004 (95% CI −0.029 to 0.020) indicates that there are 0.4% fewer drop-outs overall in the venlafaxine group, and the difference is not statistically or clinically significant. The only statistically significant drop-out comparison exists for drop-outs due to side-effects compared with the 'other drug' category, where there is a risk difference of 0.221 (95% CI 0.065–0.376), giving an NNT of 5 (95% CI 3–15) in favour of

Table 3 Response analysis

Class	Comparator	Odds ratio	95% CI	Study
TCA	Amitriptyline	1.02	0.4–2.62	Gentil *et al*, 2000
	Pooled amitriptyline	1.02	0.4–2.62	
	Clomipramine	0.54	0.21–1.36	Smeraldi *et al*, 1998
	Clomipramine	1.92	0.8–4.64	Samuelian & Hackett, 1998
	Pooled clomipramine	1.02	0.57–1.83	
	Dothiepin	1.04	0.41–2.63	Mahapatra & Hackett, 1997
	Pooled dothiepin	1.04	0.41–2.63	
	Imipramine	1.72	1.04–2.87	Shrivastava *et al*, 1994
	Imipramine	0.76	0.39–1.47	Benkert *et al*, 1996
	Imipramine	2.55	1.1–6.14	Lecrubier *et al*, 1997
	Imipramine	2.18	0.79–6.14	Schweizer *et al*, 1994
	Pooled imipramine	1.51	1.10–2.07	
	Pooled TCA	1.29	0.89–1.85	
SSRI	Fluoxetine	0.99	0.55–1.78	Costa & Silva, 1998
	Fluoxetine	0.82	0.47–1.43	Tylee *et al*, 1997
	Fluoxetine	0.54	0.33–0.87	Dierick *et al*, 1996
	Fluoxetine	1.59	0.96–2.64	Rudolph *et al*, 1998
	Fluoxetine	1.29	0.74–2.27	Silverstone & Ravindran, 1999
	Fluoxetine	1.42	0.79–2.56	Schatzberg & Cantillon, 2000
	Fluoxetine	1.32	0.73–2.39	Rudolph & Feiger, 1999
	Fluoxetine	0.97	0.47–1.97	Unpublished data[1]
	Fluoxetine	2.63	1.2–5.82	Geerts *et al*, 1999
	Fluoxetine	1.44	0.6–3.5	Tzanakaki *et al*, 2000
	Fluoxetine	2.26	0.64–9.05	Alves *et al*, 1999
	Fluoxetine	2.67	0.86–8.45	Clerc *et al*, 1994
	Pooled fluoxetine	1.17	0.99–1.38	
	Fluvoxamine	1.41	0.51–3.82	Unpublished data[2]
	Pooled fluvoxamine	1.41	0.51–3.82	
	Paroxetine	1.01	0.58–1.75	McPartlin *et al*, 1998
	Paroxetine	1.49	0.68–3.29	Poirier & Boyer, 1999
	Paroxetine	1.15	0.43–3.07	Ballus *et al*, 2000
	Pooled paroxetine	1.14	0.78–1.67	
	Sertraline	2.27	0.88–6.08	Mehtonen *et al*, 2000
	Pooled sertraline	2.27	0.88–6.08	
	Pooled SSRI	1.26	1.02–1.58	
Other	Mirtazapine	0.65	0.33–1.31	Guelfi, 1999
	Pooled mirtazapine	0.65	0.33–1.31	
	Trazodone	1.7	0.78–3.75	Cunningham *et al*, 1994
	Trazodone	2.06	0.89–4.78	Smeraldi *et al*, 1998
	Pooled trazodone	1.88	1.11–3.17	
	Pooled 'other drug'	1.28	0.43–4.31	
	Overall pooled	1.27	1.07–1.52	

TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor.
1. Unpublished data: Kornaat, H. (1998) Randomised, double-blind comparison of venlafaxine and fluoxetine for moderately depressed outpatients (abstract PM02021). XXIth Congress of the Collegium Internationale Neuro-Psychopharmacologicum, Glasgow, UK.
2. Unpublished data: Hackett D., Salinas, E. & Desmet, A. (1998) Efficacy and safety of venlafaxine vs. fluvoxamine in outpatients with major depression (abstract P1.210). IIth European Congress of Neuropsychopharmacology, Paris, France.

other drugs. However, because the overall difference in drop-out is equivalent, this result is countered by drop-out for all other causes.

DISCUSSION

Efficacy

This meta-analysis provides evidence that in the treatment of depressive disorders all antidepressants are not equal. Pooling data from all currently available studies reveals that venlafaxine carries an advantage of about 1.2 HRSD points over other antidepressants. The majority of comparisons were with SSRIs, where the effect appeared consistent across the different drugs. In contrast, it is less clear that the advantage is consistent across other antidepressants such as TCAs, where imipramine is the only individual drug that clearly demonstrates lesser efficacy. This does not, however, reduce the importance of the findings for the primary outcome measure – venlafaxine *v.* any other antidepressant in reducing symptoms of depression – in which a clear advantage was identified.

The results are of probable clinical significance, with an NNT of 19 (95% CI 11–63) for response and 14 (95% CI 9–29) for remission. The two data-sets do not include all of the same studies and are not as comprehensive as the data used in primary analysis of effect sizes, so the absolute figures must be viewed as approximate. However, this magnitude of advantage for venlafaxine over other antidepressants is potentially of considerable importance, given the often prolonged or even chronic nature of depressive episodes. It is increasingly recognised that improvement of depression on antidepressants is often incomplete or partial so that remission rates are relatively low (Ferrier, 1999) and only 42% of patients in the studies that we included achieved remission by the end of the study. Patients who fail to reach remission have significantly greater continuing morbidity and higher relapse rates than those who do experience remission (Cornwall & Scott, 1997). If only one extra person reaches remission when treated with venlafaxine instead of an SSRI for every 14 patients treated, then this is a potentially important health benefit. It suggests that even if not used first line, venlafaxine should be considered for

Table 4 Remission analysis

Class	Comparator	Odds ratio	95% CI	Study
TCA	Amitriptyline	1.03	0.46–2.32	Gentil *et al*, 2000
	Pooled amitriptyline	1.03	0.46–2.32	
	Pooled TCA	1.03	0.46–2.32	
SSRI	Fluoxetine	1.15	0.52–2.57	Costa & Silva, 1998
	Fluoxetine	1.06	0.61–1.85	Tylee *et al*, 1997
	Fluoxetine	1.49	0.9–2.47	Rudolph *et al*, 1998
	Fluoxetine	1.02	0.6–1.75	Silverstone & Ravindran, 1999
	Fluoxetine	1.8	0.97–3.35	Schatzberg & Cantillon, 2000
	Fluoxetine	2.03	1.04–3.99	Rudolph & Feiger, 1999
	Fluoxetine	1.43	0.59–3.51	Unpublished data[1]
	Fluoxetine	2.17	1.02–4.62	Geerts *et al*, 1999
	Fluoxetine	1.23	0.52–2.89	Tzanakaki *et al*, 2000
	Fluoxetine	1.5	0.57–3.92	Alves *et al*, 1999
	Pooled fluoxetine	1.42	1.17–1.73	
	Fluvoxamine	0.36	0.05–2.44	Zanardi *et al*,
	Pooled fluvoxamine	0.36	0.05–2.44	
	Paroxetine	1.09	0.69–1.71	McPartlin *et al*, 1998
	Paroxetine	1.59	0.89–2.82	Salinas, 1997
	Paroxetine	2.68	1.08–6.87	Poirier & Boyer, 1999
	Paroxetine	1.47	0.57–3.85	Ballus *et al*, 2000
	Pooled paroxetine	1.4	1.05–1.88	
	Sertraline	2.57	1.15–5.82	Mehtonen *et al*, 2000
	Pooled sertraline	2.57	1.15–5.82	
	Pooled SSRI	1.43	1.21–1.71	
Other	Mirtazapine	0.69	0.33–1.43	Guelfi, 1999
	Pooled mirtazapine	0.69	0.33–1.43	
	Pooled 'other drug'	0.69	0.33–1.43	
	Overall pooled	1.36	1.14–1.61	

TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor.
1. Unpublished data: Kennast, H. (1998) Randomised, double-blind comparison of venlafaxine and fluoxetine for moderately depressed outpatients (abstract PM02021). XXIth Congress of the Collegium Internationale Neuro-Psychopharmacologicum, Glasgow, UK.

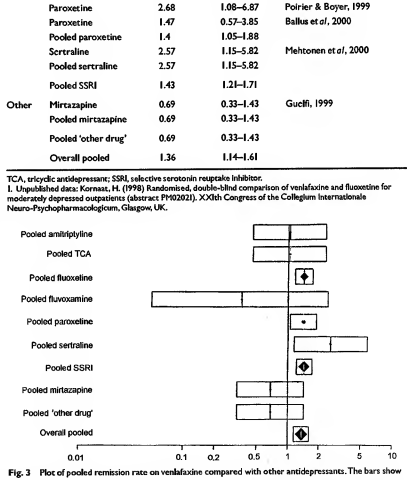

Fig. 3 Plot of pooled remission rate on venlafaxine compared with other antidepressants. The bars show the odds ratio and the 95% CI. Results falling to the right of the line of no effect (1) indicate an advantage to venlafaxine.

Table 5 Drop-out analysis by cause and drug class

	Risk difference (venlafaxine minus comparator)	Lower CL	Upper CL	NNT[1]	Lower CL	Upper CL
All causes						
All drugs	−0.004	−0.029	0.020	−224	−34	49
SSRI	0.002	−0.025	0.029	494	−40	34
TCA	−0.028	−0.089	0.033	−36	−11	30
Other drug	−0.080	−0.196	0.035	−12	−5	28
Unsatisfactory response						
All drugs	−0.006	−0.016	0.004	−159	−62	275
SSRI	−0.008	−0.019	0.003	−123	−52	350
TCA	0.003	−0.020	0.026	341	−50	39
Other drug	−0.032	−0.123	0.059	−31	−8	17
Side-effects						
All drugs	0.010	−0.007	0.026	105	−141	38
SSRI	0.017	−0.006	0.040	60	−161	25
TCA	−0.025	−0.070	0.020	−40	−14	51
Other drug	0.221	0.065	0.376	5	15	3

CL, confidence limit; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
1. A negative number needed to treat (NNT) represents the number of people that, when treated with venlafaxine, will lead to one fewer expected drop-outs v. the comparator (e.g. for all drugs and all causes of drop-out, it is expected that for every 224 people treated with venlafaxine there will be one fewer drop-outs compared with other therapies). A positive NNT represents the number of people that, when treated with venlafaxine, will lead to one more expected drop-out v. the comparator (e.g. for SSRI, all causes, it is expected that when 494 people are treated with venlafaxine, there will be one more drop-out in the venlafaxine-treated patients).

patients having an inadequate response to other antidepressants.

Our study confirms the more limited meta-analysis recently reported by Thase *et al* (2001), which only included a small subset (eight) of studies against SSRIs and therefore cannot be considered systematic. It only assessed efficacy using remission rates with an odds ratio of 1.5 (95% CI 1.3–1.9) in favour of venlafaxine. The NNT was not calculated formally but appears to be about 10 from the difference in remission rates (45% *v.* 35%); this is a greater advantage to venlafaxine than we found with a larger data-set.

Our analysis of the tolerability of venlafaxine as measured by total treatment drop-outs and those due to side-effects did not suggest that greater efficacy was offset by poorer tolerability overall or against SSRIs or TCAs. More patients dropped out of treatment owing to side-effects on venlafaxine than trazodone or mirtazapine, suggesting poorer tolerability than these drugs, but the small number of studies makes it difficult to draw conclusions.

Mechanism underlying venlafaxine's greater efficacy

We have reported previously being unable to identify a relationship between pharmacology and efficacy using a meta-regression analysis of a variety of antidepressants compared with SSRIs (Freemantle *et al*, 2000). There were, however, considerable problems in that analysis, relating to being able to identify accurately the acute pharmacology of many antidepressants *in vivo*. In this study some of these problems are overcome through using a single agent and it appears that the most plausible mechanism by which venlafaxine may exert increased efficacy in comparison with SSRIs is its ability to inhibit not only 5-HT reuptake but also the reuptake of noradrenalin (Holliday & Benfield, 1995). Whether this is the mechanism in the case of venlafaxine has yet to be confirmed, however. The profile of its binding to human monoamine transporters suggests a weak affinity for the noradrenalin transporter compared with the 5-HT transporter (Owens *et al*, 1997; Tatsumi *et al*, 1997). At lower doses, venlafaxine appears to act as an SSRI and it is unclear at what dose significant noradrenalin effects occur. Preliminary evidence suggests that, at least outside the brain, this is somewhere between 75 and 225 mg, with one study suggesting that it may occur by 150 mg (Abdelmawla *et al*, 1999). It is of interest that previous meta-analyses have suggested superior efficacy for amitriptyline against other antidepressants, particularly SSRIs (Anderson, 2000; Barbui & Hotopf, 2001), which adds some support to dual action conferring greater efficacy than occurs when blocking the reuptake of a single transmitter.

We did not find an effect of dose on the size of the advantage to venlafaxine over SSRIs, raising some question as to the mechanism underlying its greater efficacy. However, the studies in this meta-analysis were not designed to detect dose–response effects, most employing flexible dosing. The lack of an association between efficacy and a venlafaxine dose below or above 150 mg is probably against a strong linear dose–response over the range used but cannot rule out a non-linear relationship. Two fixed-dose studies of venlafaxine against placebo have suggested a dose–response over the range 60–225 mg (Kelsey, 1996; Rudolph *et al*, 1998), but the differentiation between doses has not been statistically significant and the dose at which any possible greater efficacy may arise is not clear.

Methodological considerations

The major methodological challenge to all systematic overviews is publication bias – the selective availability of trials with positive results. The comprehensive search strategies used to identify trials, the

systematic attempts to identify unpublished trials and unpublished data and examination of the distribution of the results from included trials all mediate against the importance of this threat to the validity of the results of this overview. However, it has to be acknowledged that the majority of studies were sponsored by the company that markets venlafaxine and sponsorship has been suggested as a potential factor influencing the outcome of the trials (Stewart & Parmar, 1996; Freemantle *et al*, 2000).

Although over 5000 patients were included in the trials identified for this meta-analysis, this number is small against other clinical areas where this number of patients commonly may be included in a single trial. Further randomised trials, including those of a naturalistic design, involving larger numbers of patients in different clinical settings (particularly primary care, where the majority of treatment for major depressive disorder is conducted) are required to find out how generalisable this result is to different settings and whether venlafaxine has increased effectiveness in usual clinical practice.

REFERENCES

Abdelmawla, A., Langley, R., Szabadi, E., *et al* (1999) Comparison of the effects of venlafaxine, desipramine and paroxetine on noradrenalin and methoxamine evoked constriction of the dorsal hand vein. *British Journal of Clinical Pharmacology*, **48**, 345–354.

American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders* (4th edn) (DSM–IV). Washington, DC: APA.

Anderson, I. M. (2000) Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *Journal of Affective Disorders*, **58**, 19–36.

—, Nutt, D. J. & Deakin, J. F.W. (2000) Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology guidelines. *Journal of Psychopharmacology*, **14**, 3–20.

Barbui, C. & Hotopf, M. (2001) Amitriptyline v. the rest: still the leading antidepressant after 40 years of randomised controlled trials. *British Journal of Psychiatry*, **178**, 129–144.

Cornwall, P. & Scott, J. (1997) Partial remission in depressive disorders. *Acta Psychiatrica Scandinavica*, **95**, 265–271.

DerSimonian, R. & Laird, N. (1986) Meta-analysis in clinical trials. *Controlled Clinical Trials*, **7**, 177–188.

Eccles, M., Freemantle, N. & Mason, J. (2000) The choice of antidepressants for depression in primary care. *Family Practice*, **16**, 103–111.

Edwards, G. (1992) Selective serotonin reuptake inhibitors: a modest though welcome advance in the treatment of depression. *BMJ*, **304**, 1644–1645.

Ferrier, N. (1999) Treatment of major depression: is improvement enough? *Journal of Clinical Psychiatry*, **60** (suppl. 6), 10–14.

Freemantle, N., Cleland, J., Young, P., *et al* (1999) What is the current place of β-blockade in secondary prevention after myocardial infarction? A systematic overview and meta regression analysis. *BMJ*, **318**, 1730–1737.

—, Anderson, I. M. & Young, P. (2000) Predictive value of pharmacological activity for the relative efficacy of antidepressant drugs. Meta-regression analysis. *British Journal of Psychiatry*, **177**, 292–302.

Geddes, J. R., Freemantle, N., Mason, J., *et al* (2001) SSRIs versus alternative antidepressants for depressive disorders. *Cochrane Library*, issue 1. Oxford: Update Software.

Gross, G. & Huber, G. (1999) How far are newer antidepressants an advance compared with classical antidepressants? *Neurology, Psychiatry and Brain Research*, **7**, 79–86.

Guy, W. (1976) *ECDEU Assessment Manual for Psychopharmacology*. Revised DHEW Pub. (ADM). Rockville, MD: National Institute for Mental Health.

Hamilton, M. (1960) A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*, **23**, 56–62.

Heninger, G., Delgado, P. & Charney, D. (1996) The revised monoamine theory of depression: a modulatory role of monoamines, based on new findings from monoamine depletion experiments in humans. *Pharmacopsychiatry*, **29**, 2–11.

Holliday, S. M. & Benfield, P. (1995) Venlafaxine. A review of its pharmacology and therapeutic potential in depression. *Drugs*, **49**, 280–294.

Kelsey, J. (1996) Dose–response relationship with venlafaxine. *Journal of Clinical Psychopharmacology*, **16** (suppl. 2), 21S–26S.

Montgomery, S. A. & Åsberg, M. (1979) A new depression scale designed to be sensitive to change. *British Journal of Psychiatry*, **134**, 382–389.

Murray, C. & Lopez, A. (1997) Global mortality, disability, and the contribution of risk factors: global burden of disease study. *Lancet*, **349**, 1436–1442.

Nelson, J. Mazure, C., Bowers, M., *et al* (1991) A preliminary, open study of the combination of fluoxetine and desipramine for rapid treatment of major depression. *Archives of General Psychiatry*, **48**, 303–307.

Owens, M., Morgan, W., Plott, S., *et al* (1997) Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites. *Journal of Pharmacological Experimental Therapies*, **283**, 1305–1322.

Rudolph, R., Fabre, L., Feighner, J., *et al* (1998) A randomised, placebo-controlled, dose–response trial of venlafaxine hydrochloride in the treatment of major depression. *Clinical Psychiatry*, **59**, 116–122.

Seth, R., Jennings, A. L., Bindman, J., *et al* (1992) Combination treatment of noradrenalin and serotonin reuptake inhibitors in resistant depression. *British Journal of Psychiatry*, **161**, 562–565.

Smith, T., Spiegelhalter, D. & Thomas, A. (1995) Bayesian approaches to random-effects meta-analysis: a comparative study. *Statistics in Medicine*, **14**, 2685–2699.

Stewart, L. A. & Parmar, M. K. B. (1996) Bias in the analysis and reporting of randomized controlled trials. *International Journal of Technology Assessment in Health Care*, **12**, 264–275.

Tatsumi, M., Groshan, K., Blakely, R., *et al* (1997) Pharmacological profile of antidepressants and related compounds at human monoamine transporters. *European Journal of Pharmacology*, **340**, 249–258.

Thase, M. E., Entsuah, A. R. & Rudolph, R. L. (2001) Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *British Journal of Psychiatry*, **178**, 234–241.

APPENDIX

Studies included in the meta-analysis

Alves, C., Cachola, I. & Brandao, J. (1999) Efficacy and tolerability of venlafaxine and fluoxetine in outpatients with major depression. *Primary Care Psychiatry*, **5**, 57–63.

Ballus, C., Quiros, G., de-Flores, T., *et al* (2000) The efficacy and tolerability of venlafaxine and paroxetine in outpatients with depressive disorder of dysthymia. *International Clinical Psychopharmacology*, **15**, 43–48.

Benkert, O., Gruender, G., Wetzel, H., *et al* (1996) A randomised, double-blind comparison of a rapidly escalating dose of venlafaxine and imipramine in inpatients with major depression and melancholia. *Journal of Psychiatric Research*, **30**, 441–451.

Clerc, G. E., Ruimy, P. & Verdeau, P. J. (1994) A double-blind comparison of venlafaxine and fluoxetine in patients hospitalised for major depression and melancholia. *International Clinical Psychopharmacology*, **9**, 139–143.

Costa, E. & Silva, J. (1998) Randomised, double-blind comparison of venlafaxine and fluoxetine in outpatients with major depression. *Journal of Clinical Psychiatry*, **59**, 352–357.

Cunningham, L., Borison, R., Carman, J., *et al* (1994) A comparison of venlafaxine, trazodone and placebo in major depression. *Journal of Clinical Psychopharmacology*, **14**, 99–106.

Dierick, M., Raviteau, L., Realini, R., *et al* (1996) A double-blind comparison of venlafaxine and fluoxetine for treatment of major depression in outpatients. *Progress in NeuroPsychopharmacology and Biological Psychiatry*, **20**, 57–71.

Geerts, S., Lacante, P. & Migon, A. (1999) Venlafaxine versus fluoxetine in the treatment of depressed patients with concomitant anxiety. *Journal of the European College of Neuropsychopharmacology*, **9** (suppl. 5), S224.

Gentil, V., Kerr-Correa, F., Moreno, R., *et al* (2000) Double-blind comparison of venlafaxine and amitriptyline in outpatients with major depression with or without melancholia. *Journal of Psychopharmacology*, **14**, 61–66.

Guelfi, J. D. (1999) *Efficacy and Tolerability of Mirtazapine versus Venlafaxine in Hospitalised, Severely Depressed Patients with Melancholia* [Abstract]. London: Association of Clinical Neuropsychopharmacology.

Lecrubier, Y., Bourin, M., Moon, C-A.L., *et al* (1997) Efficacy of venlafaxine in depressive illness in general practice. *Acta Psychiatrica Scandinavica*, **95**, 485–493.

McPartlin, G. M., Reynolds, A., Anderson, C., *et al* (1998) A comparison of once-daily venlafaxine XR and paroxetine in depressed outpatients treated in general practice. *Primary Care Psychiatry*, **693**, 127–132.

Mahapatra, S. N. & Hackett, D. (1997) A randomised, double-blind, parallel-group comparison of venlafaxine and dothiepin in geriatric patients with

major depression. *International Journal of Clinical Practice*, **51**, 209–213.

Mehtonen, O., Sogaard, J., Roponen, P., et al (2000) Randomized, double-blind comparison of venlafaxine and sertraline in outpatients with major depressive disorder. *Journal of Clinical Psychiatry*, **61**, 95–100.

Poirier, M. F. & Boyer, P. (1999) Venlafaxine and paroxetine in treatment-resistant depression. Double-blind, randomised comparison. *British Journal of Psychiatry*, **175**, 12–16.

Rudolph R., Fabre, L., Feighner, J., et al (1998) A randomised, placebo-controlled, dose–response trial of venlafaxine hydrochloride in the treatment of major depression. *Clinical Psychiatry*, **59**, 116–122.

—— & Feiger, A. (1999) A double-blind, randomised, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. *Journal of Affective Disorders*, **56**, 171–181.

Salinas, E. (1997) Once-daily venlafaxine XR versus paroxetine outpatients with major depression. *Biological Psychiatry*, **42** (suppl. 1), 297S.

Samuelian, J. C. & Hackett, D. (1998) A randomised, double-blind, parallel-group comparison of venlafaxine and clomipramine in outpatients with major depression. *Journal of Psychopharmacology*, **12**, 273–278.

Schatzberg, A. & Cantillon, M. (2000) Antidepressant early response and remission with venlafaxine or fluoxetine in depressed geriatric patients. *International Journal of Neuropsychopharmacology*, **3** (suppl. 1), S191.

Schweizer, E., Feighner, J., Mandos, L. A., et al (1994) Comparison of venlafaxine and imipramine in the acute treatment of major depression in outpatients. *Journal of Clinical Psychiatry*, **55**, 104–108.

Shrivastava, R. K., Cohn, C., Crowder, J., et al (1994) Long-term safety and clinical acceptability of venlafaxine and imipramine in outpatients with major depression. *Journal of Clinical Psychopharmacology*, **14**, 322–329.

Silverstone, P. H. & Ravindran, A. (1999) Once-daily venlafaxine extended release (XR) compared with fluoxetine in outpatients with depression and anxiety. Venlafaxine XR 360 Study Group. *Journal of Clinical Psychiatry*, **60**, 22–28.

Smeraldi, E., Rizzo, F. & Crespi, G. (1998) Double-blind, randomised study of venlafaxine, clomipramine and trazodone in geriatric patients with major depression. *Primary Care Psychiatry*, **4**, 189–195.

Stanley, N., Kimber, S., Fairweather, D., et al (1998) Venlafaxine and dothiepin in depressed patients: a comparison of efficacy and effect on cognition and subjective sleep [Abstract P1044]. *11th European Congress of Neuropsychopharmacology*. Paris, France.

Tylee, A., Beaumont, G., Bowden, M. W., et al (1997) A double-blind, randomised, 12-week comparison study of the safety and efficacy of venlafaxine and fluoxetine in moderate to severe depression in general practice. *Primary Care Psychiatry*, **3**, 51–58.

Tzanakaki, M., Guazzelli, M., Nimatoudis, I., et al (2000) Increased remission rates with venlafaxine compared with fluoxetine in hospitalised patients with major depression and melancholia. *International Clinical Psychopharmacology*, **15**, 29–34.

Zanardi, R., Franchini, L., Serretti, A., et al (2000) Venlafaxine versus fluvoxamine in the treatment of delusional depression: a pilot double-blind controlled study. *Journal of Clinical Psychiatry*, **61**, 26–29.

CLINICAL IMPLICATIONS

- The findings from this systematic review and meta-analysis provide some confidence that venlafaxine is more effective than selective serotonin reuptake inhibitors (SSRIs) with comparable tolerability.
- The size of this advantage is of probable clinical importance when the prolonged or chronic nature of depression is taken into account.
- Venlafaxine should be considered for patients in whom efficacy needs to be maximised and in those failing to respond to an SSRI.

LIMITATIONS

- Apart from the comparison with fluoxetine, there are insufficient comparisons between venlafaxine and individual SSRIs and other antidepressants to draw strong conclusions with regard to specific comparisons.
- Meta-analysis is dependent on the quality of individual studies included in the analysis.
- Drop-outs are a relatively crude proxy for tolerability.

DAVID SMITH, PhD, Kaiser Center for Health Research, Portland, Oregon, USA; CARRIE DEMPSTER, MSc, University of Dumfries and Galloway, Scotland; JULIE GLANVILLE, MSc, NHS Centre for Reviews and Dissemination, University of York; NICK FREEMANTLE, PhD, Department of Primary Care & General Practice, University of Birmingham; IAN ANDERSON, MD, Neuroscience and Psychiatry Unit, University of Manchester, UK

Correspondence: Nick Freemantle, Department of Primary Care and General Practice, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK. Tel: +44 (0)121 414 7943; fax: +44 (0)121 414 6571; e-mail: N.Freemantle@bham.ac.uk

(First received 8 July 2001, final revision 18 January 2002, accepted 31 January 2002)

Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors

MICHAEL E. THASE, A. RICHARD ENTSUAH and RICHARD L. RUDOLPH

Background It had been suggested that the antidepressant venlafaxine, which inhibits reuptake of both serotonin and (at higher doses) noradrenaline, may result in better outcomes than treatment with selective serotonin reuptake inhibitors (SSRIs).

Aims To compare remission rates during treatment with SSRIs or venlafaxine.

Method Data from eight comparable randomised, double-blind studies of major depressive disorder were pooled to compare remission rates (Hamilton Rating Scale for Depression score ⩽7) during treatment with venlafaxine (n=851), SSRIs (fluoxetine, paroxetine, fluvoxamine; n=748) or placebo (four studies; n=446).

Results Remission rates were: venlafaxine, 45% (382/851); SSRIs, 35% (260/748); placebo, 25% (110/446) ($P<0.001$; odds ratio for remission is 1.50 (1.3–1.9), favouring venlafaxine v. SSRIs). The difference between venlafaxine and the SSRIs was significant at week 2, whereas the difference between SSRIs and placebo reached significance at week 4. Results were not dependent on any one study or the definition of remission.

Conclusions Remission rates were significantly higher with venlafaxine than with an SSRI.

Declaration of interest M.E.T. is a paid consultant to Wyeth–Ayerst Laboratories, the employer of A.R.E. and R.L.R.

The more commonly used measure of antidepressant efficacy in clinical trials has been a 50% reduction from baseline total scores on the Hamilton Rating Scale for Depression (HRSD) (Prien *et al*, 1991; Depression Guideline Panel, 1993). A more stringent measure of antidepressant efficacy is the ability to induce remission, a clinical state characterised by minimal residual symptoms (e.g. 17-item HRSD total scores of ⩽7; Frank *et al*, 1991). Patients treated to full remission are less likely to relapse (Thase *et al*, 1992; Fava *et al*, 1996) and have more normal psychosocial and vocational functioning (Miller *et al*, 1998) when compared with incompletely remitted patients. This report presents the results of a pooled analysis of remission rates comparing venlafaxine and three selective serotonin reuptake inhibitors (SSRIs): fluoxetine, paroxetine and fluvoxamine. It includes original data from 2045 patients with depression, drawn from eight related randomised controlled trials. We undertook this analysis to test the hypothesis that patients treated with venlafaxine, a serotonin–noradrenaline reuptake inhibitor (SNRI) (Muth *et al*, 1986), are significantly more likely to achieve remission than those treated with SSRIs.

METHOD

This analysis included data from the patients with depression who participated in the eight double-blind, randomised clinical trials comparing venlafaxine and SSRIs conducted by the Clinical Research and Development department at Wyeth–Ayerst Laboratories during the development of the immediate-release (IR) and extended-release (XR) formulations of venlafaxine. Results from four of these studies have been published (Clerc *et al*, 1994; Dierick *et al*, 1996; Silverstone *et al*, 1998; Rudolph & Feiger, 1999). Results from two studies have been presented as posters and published in abstract form (Salinas *et al*, 1997; Rudolph *et al*, 1998*a*). The remaining two studies are unpublished (Studies 347 and 349; data on file, Wyeth–Ayerst Laboratories, Philadelphia, PA). The doses employed were: venlafaxine IR, 75–375 mg/day; venlafaxine XR, 75–225 mg/day; fluoxetine, 20–80 mg/day; paroxetine, 20–40 mg/day; and fluvoxamine, 100–200 mg/day. Four studies included a placebo control group (Salinas *et al*, 1997; Rudolph *et al*, 1998*a*; Silverstone *et al*, 1998; Rudolph & Feiger, 1999). Each study was approved by the ethics committees of the participating sites and conducted according to the guidelines of the Declaration of Helsinki and its amendments. All patients provided written informed consent. Table 1 summarises the study characteristics.

Patients

Patients could be enrolled if they were at least 18 years old and met the criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM; American Psychiatric Association, 1987, 1994) for major depression (DSM–III–R) or major depressive disorder (DSM–IV) for at least 1 month. There were 68 in-patients (one study, Clerc *et al*, 1994) and 1977 out-patients; all patients had minimum scores of either 20 on the $HRSD_{21}$ (Hamilton, 1960) or 25 on the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979) at both pre-study and baseline (study day −1), with no greater than a 20% decrease in severity between pre-study and baseline evaluations.

Patients with clinically significant cardiovascular, renal or hepatic disease, seizure disorders, a recent history of alcohol or drug misuse or clinically significant abnormalities on baseline physical examination, electrocardiogram (ECG) or laboratory tests were excluded from participation. Patients who were hypersensitive to the study drugs or had used any investigational or antipsychotic drug within 30 days, a monoamine oxidase inhibitor within 14 days or other antidepressant, anxiolytic, sedative–hypnotic or non-psychopharmacological drugs with psychotropic effects within 7 days of double-blind treatment also were excluded. Chloral hydrate (maximum 2000 mg) or temazepam (20 mg; one study) were permitted as hypnotics. Table 2 summarises the

Table 1 Studies pooled for analysis of the Hamilton Rating Scale for Depression remission (n=8)

Study	Treatment	Dosage range (mean)	Number of patients per study: all patients (n=2117)/ITT (n=2045)	Treatment duration (weeks)
Rudolph & Feiger, 1999 (Study 211)	Venlafaxine XR	75–225 mg/day (175)	100/95	8
	Fluoxetine	20–60 mg/day (47)	103/103	
	Placebo		98/97	
Silverstone *et al*, 1999 (Study 360)	Venlafaxine XR	75–225 mg/day (141)	128/121	8[2]
	Fluoxetine	20–60 mg/day (40)	121/114	
	Placebo		118/118	
Salinas *et al*, 1997 (Study 367)	Venlafaxine XR	75–150 mg/day (75/150)[1]	165/161	8
	Paroxetine	20 mg/day (20)	81/80	
	Placebo		83/82	
Rudolph *et al*, 1998a (Study 372)	Venlafaxine IR	75–375 mg/day (318)	156/144	6
	Fluoxetine	20–80 mg/day (NA)	152/146	
	Placebo		152/149	
Clerc *et al*, 1994 (Study 340)	Venlafaxine IR	100–200 mg/day (199)	34/33	6
	Fluoxetine	20–40 mg/day (NA)	34/34	
Study 347[3]	Venlafaxine IR	75–150 mg/day (NA)	77/77	6
	Fluvoxamine	100–200 mg/day (NA)	34/34	
Dierick *et al*, 1996 (Study 348)	Venlafaxine IR	75–150 mg/day (112)	153/145	8
	Fluoxetine	20 mg/day	161/157	
Study 349[3]	Venlafaxine IR	75–150 mg/day (NA)	82/75	8
	Paroxetine	20–40 mg/day (NA)	85/80	

1. This study employed 75 and 150 mg fixed doses of venlafaxine XR.
2. This study lasted 12 weeks but results are presented at week 8 for consistency.
3. Unpublished data on file, Wyeth–Ayerst Research, Philadelphia, PA.
IR, immediate-release formula; ITT, intent-to-treat patients; XR, extended-release formulation.

Table 2 Baseline characteristics of intent-to-treat patients (pooled studies, n=2045)

Characteristic	Venlafaxine (n=851)	SSRI (n=748)	Placebo (n=446)
Mean age, years (s.d.)	42 (12)	42 (13)	41 (11)
Women/men, %	65/35	64/36	62/38
Mean (s.d.) $HRSD_{21}$ total score	26 (5)	26 (4)	26 (4)
Mean (s.d.) MADRS total score	31 (5)	31 (5)	30 (5)
CGI–S score >4 (%)	53	53	36[1]

1. Studies utilising placebo enrolled significantly fewer patients with CGI–S scores >4 ($P<0.01$). Across the placebo-controlled studies there was no difference between groups.
CGI–S, Clinical Global Impression – Severity of Illness; $HRSD_{21}$, 21-item Hamilton Rating Scale for Depression; MADRS, Montgomery–Åsberg Depression Rating Scale; SSRI, selective serotonin reuptake inhibitor.

socio-demographic and pre-treatment clinical characteristics of the pooled study groups.

Study drugs

Patients were randomly assigned to treatment with venlafaxine (n=865), an SSRI (fluoxetine, n=563; paroxetine, n=160; or fluvoxamine, n=34) or placebo (four studies only, n=450) during the double-blind treatment period at the daily dosages shown in Table 1.

Efficacy and safety assessments

The HRSD, MADRS and Clinical Global Impression – Severity of Illness (CGI–S) (National Institute of Mental Health, 1985) were performed at study day −1, prior to double-blind therapy. These measures (along with the CGI improvement score) were reassessed on study days 7, 14, 21, 28, 42 and, if available, 56. Remission was defined as a total score of $\leqslant 7$ on the first 17 items of the HRSD (Frank *et al*, 1991).

Safety and tolerability were evaluated on the basis of adverse events that were recorded throughout the study evaluation period and changes that occurred in the physical examination, vital signs, 12-lead ECG recordings and clinical laboratory tests during treatment. For this report, only the proportions of patients withdrawn from double-blind therapy because of side-effects and lack of efficacy were compared.

Statistical analyses

The analyses were performed on data from a modified intent-to-treat sample, which included all patients who received at least one dose of study medication and had at least one HRSD evaluation during therapy. Remission rates were calculated using the last-observation-carried-forward (LOCF)

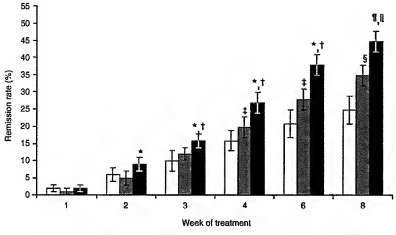

Fig. 1 Remission rates ($HRSD_{17}$ score $\leq 7 \pm 95\%$ CI) for pooled studies comparing venlafaxine (black bar), SSRI (grey bar) and placebo (white bar) treatments: *$P \leq 0.05$, venlafaxine v. SSRI; †$P \leq 0.05$, venlafaxine v. placebo; ‡$P \leq 0.05$, SSRI v. placebo; §$P < 0.001$, SSRI v. placebo; ¶$P < 0.001$, venlafaxine v. SSRI; ‖$P < 0.001$, venlafaxine v. placebo. $HRSD_{17}$, 17-item Hamilton Rating Scale for Depression; SSRI, selective serotonin reuptake inhibitor.

method, which allowed the inclusion of patients who were withdrawn early. Pairwise comparisons of remission rates were made with Fisher's exact test. All tests of hypotheses were two-sided. Results of statistical analyses were considered significant when P was ≤ 0.05. The 95% confidence intervals (CIs) for differences in remission rates between groups were calculated for the pooled data at each interval. The odds ratios for remission with a 95% CI (Rothman, 1986) were also calculated for venlafaxine or an SSRI *v.* placebo and for venlafaxine *v.* the SSRIs. Homogeneity of the odds ratios across studies was tested with the Breslow–Day test (Breslow & Day, 1980).

Analyses of various subgroups were performed to corroborate the overall findings, including studies using the extended-release or immediate-release formulations, active-controlled studies, placebo-controlled studies, the single in-patient study, the seven out-patient studies and studies utilising fluoxetine *v.* those using other SSRIs. Additional analyses compared alternative definitions of remission to ensure the robustness of the findings. The following additional definitions were examined: $HRSD_{21} \leq 7$, $HRSD_{21} \leq 8$, $HRSD_{21} \leq 10$, $HRSD_{17} \leq 10$ plus CGI=1, MADRS <10, and $\geq 50\%$ decrease from baseline $HRSD_{21}$ scores. Finally, a sensitivity analysis was performed by removing each individual study from the pooled analysis, one at a time (Thase *et al*, 1997).

RESULTS

Among the 2117 patients enrolled, 2045 (96.6%) were included in the intent-to-treat analyses of venlafaxine IR and venlafaxine XR (n=851), the SSRIs (n=748) and placebo (n=446). Results from one investigational site (27 patients in total) were excluded prior to the analysis because the validity of the data could not be verified. The treatment groups had similar characteristics at baseline (see Table 2). However, patients enrolled in the four placebo-controlled studies were significantly less severely depressed than those enrolled in the other studies.

Final remission rates were 45% for venlafaxine (382/851), 35% for the SSRIs (260/748) and 25% for placebo (110/446). The differences for venlafaxine *v.* SSRIs, venlafaxine *v.* placebo and SSRIs *v.* placebo were highly statistically significant ($P < 0.001$ for all comparisons).

Week-by-week comparisons are illustrated in Fig. 1. Venlafaxine was statistically significantly more effective than the SSRIs from week 2 onwards and versus placebo from week 3 onwards. The SSRI group had a significantly higher remission rate

Table 3 Remission rates (%) and odds ratios for comparison of intent-to-treat 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$) remission by treatment[1]

Study	Remission rate (%)			Odds ratio		
	Venlafaxine	SSRI	Placebo	Venlafaxine *v.* SSRI	Venlafaxine *v.* placebo	SSRI *v.* placebo
Rudolph & Feiger, 1999 (Study 211)	42	23	23	2.4	2.5	1.0
Silverstone *et al*, 1999 (Study 360)	29	28	14	1.1	2.4	2.3
Salinas *et al*, 1997 (Study 367)	49[3]	36	38	1.9	1.6	1.1
Rudolph *et al*, 1998*a* (Study 372)	44	34	23	1.5	2.5	1.7
Clerc *et al*, 1994 (Study 340)	55	26	–	3.5	–	–
Study 347[2]	51	35	–	1.9	–	–
Dierick *et al*, 1996 (Study 348)	52	45	–	1.3	–	–
Study 349[2]	35	35	–	1.0	–	–
Pooled data	45	35	25	1.5	2.2	1.4

1. The remission rates reported here reflect the intent-to-treat, $HRSD_{17} \leq 7$ method used in this paper. The results may therefore differ from those reported in the source manuscripts.
2. Unpublished data on file, Wyeth–Ayerst Research, Philadelphia, PA.
3. The intent-to-treat remission rate on 75 mg/day of venlafaxine XR was 47% and on 150 mg/day it was 51%.
SSRI, selective serotonin reuptake inhibitor.

than the placebo group from week 4 onwards.

The results of the eight individual studies are summarised in Table 3. Odds ratios for remission ranged from 1.0 to 3.5, with an overall odds ratio of 1.5 (95% CI 1.3–1.9). Thus, there was a 50% greater chance of remission during venlafaxine treatment than during SSRI treatment. Testing for homogeneity of the odds ratios revealed no significant difference (χ^2=8.63, d.f.=7, P=0.28). The sensitivity analysis similarly found that the significant difference between venlafaxine and the SSRIs was not dependent on any one study.

Figure 2 illustrates the results for various subgroup comparisons. The differences between venlafaxine and the SSRIs were statistically significant for all but one of the subgroup analyses. The comparison of venlafaxine and SSRI that included only the four studies that were not placebo-controlled was not statistically significant (P=0.055).

Figure 3 summarises the results according to multiple alternative outcome criteria. Regardless of the definition used, venlafaxine was significantly more effective than the SSRIs, and the SSRIs were significantly more effective than placebo.

In total, 83 (9%) patients were withdrawn from venlafaxine therapy because of side-effects, compared with 57 (7%) SSRI-treated patients and 10 (2%) patients given placebo (Fisher's exact test, P=0.001, venlafaxine *v.* placebo and SSRI *v.* placebo; the venlafaxine *v.* SSRI comparison was not significant, P=0.185). A total of 33/895 (4%) of the venlafaxine-treated patients were withdrawn because of lack of efficacy, compared with 46/769 (6%) of patients given an SSRI and 63/453 (14%) of patients given placebo (Fisher's exact test, P=0.037, venlafaxine *v.* SSRI; P=0.001, venlafaxine *v.* placebo; P=0.001, SSRI *v.* placebo).

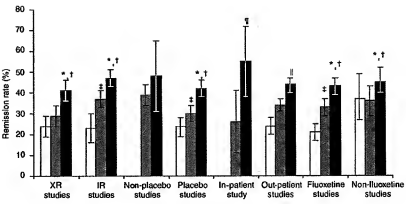

Fig. 2 Remission rates (HRSD$_{17}$ score ≤7; ±95% CI) in different study types: *P=0.0009 (XR studies), P=0.003 (immediate-release studies) and P=0.0003 (placebo studies) (white bar), venlafaxine (black bar) *v.* SSRI (grey bar); †P < 0.001 (XR studies) and P < 0.0001 (immediate-release studies, placebo studies), venlafaxine *v.* placebo (white bar); ‡P=0.028 (immediate-release studies, placebo studies), SSRI *v.* placebo; §P=0.055, venlafaxine *v.* SSRI; ¶P=0.026 (in-patient study), venlafaxine *v.* SSRI; ‖P=0.002 (out-patient studies), venlafaxine *v.* SSRI. HRSD$_{17}$, 17-item Hamilton Rating Scale for Depression; XR, venlafaxine extended-release formulation; IR, venlafaxine immediate-release (conventional) formulation; SSRI, selective serotonin reuptake inhibitor.

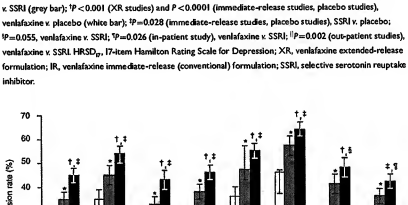

Fig. 3 Final on-therapy remission rates (mean, 95% CI) with different definitions of remission: *P < 0.001, SSRI (grey bar) *v.* placebo (white bar); †P < 0.001, venlafaxine (black bar) *v.* SSRI; ‡P < 0.001, venlafaxine *v.* placebo; §P=0.023, venlafaxine *v.* SSRI; ¶P=0.014, venlafaxine *v.* SSRI. HRSD, Hamilton Rating Scale for Depression; SSRI, selective serotonin reuptake inhibitor; MADRS, Montgomery–Åsberg Depression Rating Scale; CGI, Clinical Global Impression scale.

DISCUSSION

Are all antidepressants equally effective?

It is often stated that the various different classes of antidepressant medication are equally effective (American Psychiatric Association, 1993; Depression Guideline Panel, 1993). However, the methods used to conduct randomised clinical trials render them relatively insensitive to possible differences between active antidepressants (Thase, 1999). Studies seldom compare groups larger than 120 patients, which does not afford the statistical power to detect modest but still clinically meaningful differences. In addition, multi-site trials may have relatively lower statistical power because of greater patient heterogeneity and lower reliability of diagnoses or dependent measures (Thase, 1999). Moreover, the composition of study groups can have a marked influence on the apparent efficacy of a treatment (Quitkin *et al*, 1993; Thase *et al*, 1997).

Meta-analysis provides useful alternative methods to compare active treatments. For example, meta-analyses comparing tricyclic antidepressants and

SSRIs found differences in subgroup comparisons not apparent in qualitative reviews (Anderson & Tomenson, 1994; Edwards & Anderson, 1999). However, because the statistical power of a conventional meta-analysis is determined by the number of studies included, a large number of comparative trials must be available. For comparisons between newer antidepressants, meeting this requirement is often difficult. A second type of meta-analysis, using the data of individual patients participating in a series of related clinical trials, permits powerful comparisons to be made with a much smaller number of studies. Such pooled analyses have been used to document the efficacy of monoamine oxidase inhibitors in the treatment of atypical depression (Quitkin *et al*, 1993), to examine the association between fluoxetine and suicidality (Beasley *et al*, 1991), to examine the effects of venlafaxine treatment on blood pressure (Thase, 1998) and to compare psychotherapy and pharmacotherapy (Thase *et al*, 1997; DeRubeis *et al*, 1999).

The clinical significance of the magnitude of the differences between venlafaxine and the SSRIs warrants comment. In a conventional antidepressant clinical trial, the size of the study groups is such that statistically significant effects parallel relatively large differences in response rates (i.e. 20–25%) that are clearly clinically significant. An analysis of pooled data from an extremely large group of patients, by contrast, would have the statistical power to detect differences in remission rates so small that they would be considered trivial by most (i.e. 3–5%). The difference in remission rates observed in our pooled analysis is roughly halfway between these extremes. Given the high prevalence of depression and the staggering associated illness burden, a 10% advantage in remission rates could have substantial public health implications, particularly if costs and tolerability are comparable. From another perspective, we observed that venlafaxine-treated patients had a 50% greater chance of attaining remission than patients treated with an SSRI. In terms of the number of patients needed to treat to realise a difference, ten patients would need to be treated with venlafaxine in order to obtain one extra case of remission when compared with the SSRIs. When considered together, these various indicators point to a clinically meaningful difference.

Relationships to pharmacological mechanisms

It is proposed that the greater efficacy of venlafaxine is the result of reuptake inhibition of both serotonin and noradrenaline. Of course, reuptake inhibition is not essential to therapeutic action and it is possible that medications that potently and selectively affect either serotonergic or noradrenergic neurotransmission may initiate cascades of intracellular events that ultimately modulate the same changes in gene activity (Duman *et al*, 1997). Nevertheless, several previous studies found clomipramine, another potent dual reuptake inhibitor, to have a significant advantage relative to SSRIs (see Anderson &

Table 4 Summary of intent-to-treat remission rates of nine venlafaxine–SSRI comparative studies of non-psychotic depression not included in pooled analysis

Study	Setting	Duration (weeks)	Treatment (n)	Dosage (mg/day)	Remission criterion	ITT remission rate (%)
Tylee *et al*, 1997	PC	12	Venlafaxine IR (171)	75	MADRS ≤6	35
			Fluoxetine (170)	20		34
McPartlin *et al*, 1998	PC	12	Venlafaxine XR (183)	75	HRSD ≤6	54
			Paroxetine (178)	20		52
Diaz-Martinez *et al*, 1998	OP	8	Venlafaxine IR (70)	75–150	CGI=1	41
			Fluoxetine (75)	20–40		36
Costa e Silva, 1998[1]	OP	8	Venlafaxine IR (196)	75–150	CGI=1	58
			Fluoxetine (186)	20–40		35
					HRSD ≤7	60
						60
Poirier & Boyer, 1999	OP/IP	6	Venlafaxine IR (61)	75–300	HRSD <10	37
			Paroxetine (62)	20–40		18
Alves for the Venlafaxine Study Group (1999)	OP	12	Venlafaxine IR (40)	75–150	HRSD ≤8	30
			Fluoxetine (47)	20–40		11
Mehtonen *et al*, 2000	OP	8	Venlafaxine IR (75)	75–150	HRSD <10	53
			Sertraline (72)	50–100		38
Ballús *et al*, 2000	OP	12	Venlafaxine IR (41)	75–150	HRSD <8	59
			Paroxetine (43)	20–40		31
Tzanakaki *et al*, 2000[1]	IP/PHP	6	Venlafaxine IR (55)	225	HRSD <7	41
			Fluoxetine IR (54)	60		36
					CGI=1	51
						32

1. Results reported according to two definitions of remission.
CGI, Clinical Global Impression (improvement) scale; HRSD, Hamilton Rating Scale for Depression; IP, psychiatric in-patient; IR, immediate-release formulation; ITT, intent to treat; MADRS, Montgomery–Åsberg Depression Rating Scale; OP, psychiatric out-patient; PC, primary care; PHP, partial hospitalisation programme; XR, extended-release formulation.

Tomenson, 1994). It appears that relatively higher doses of venlafaxine may be necessary to achieve significant noradrenergic effects, as inferred from *in vitro* (Muth *et al*, 1986; Owens *et al*, 2000), animal (Redrobe *et al*, 1998) and human (Thase, 1998; Harvey *et al*, 2000) studies. Consistent with this, there is a clear dose–response relationship for venlafaxine (Rudolph *et al*, 1998*b*) and patients who fail to benefit from 75 mg/day often respond to higher doses (Dierick *et al*, 1996; Costa e Silva, 1998; Diaz-Martinez *et al*, 1998; Mehtonen *et al*, 2000). Therefore, it is likely that the difference in efficacy between venlafaxine and SSRIs is dose dependent. Unfortunately, the flexible dose schedules utilised in five of the studies included in our meta-analysis precluded a valid examination of dose–response relationships. Research using modern molecular biological techniques would help to confirm that the greater antidepressant efficacy of venlafaxine is directly linked to a dual reuptake-inhibitory mechanism of action.

Review of other comparative studies

The most important limitation of a pooled analysis is that the results can be biased by selection of a non-representative group of studies. Our data set included all eight comparative studies conducted by the Wyeth–Ayerst Clinical Research and Development department; no studies were excluded. However, there are at least 12 other studies comparing venlafaxine and SSRIs for treatment of non-psychotic depression. Among these, three recently completed studies (double-blind, placebo- and fluoxetine-controlled trials in out-patients with melancholia, in-patients with melancholia or elderly patients) could not be included because data analyses were not complete. The remaining nine published studies were not included because we did not have access to the original data sets (see Table 4).

It is possible that the inclusion of these additional trials would have affected the findings of the current pooled analysis. We therefore conducted a qualitative review of the nine published studies. Two studies found no evidence of differences in response or remission rates (Tylee *et al*, 1997; McPartlin *et al*, 1998). These studies were conducted in primary care clinics and compared the minimum therapeutic dosages of venlafaxine (75 mg/day) and fluoxetine (20 mg/day) (Tylee *et al*, 1997) or paroxetine (20 mg/day) (McPartlin *et al*, 1998).

Two studies reported non-significant differences (Diaz-Martinez *et al*, 1998; Alves *et al*, 1999). Diaz-Martinez *et al* (1998) reported that 41% of 70 patients treated with venlafaxine (75–150 mg/day) remitted during an open-label but randomised 8-week trial, as compared with 36% of 75 patients treated with fluoxetine (20–40 mg/day). The difference was 30% (i.e. 50% *v.* 20%) among those who received either 150 mg/day of venlafaxine (n=18) or 40 mg/day of fluoxetine (n=15). However, this numerically large difference was not statistically significant (P=0.07) in such a small subsample. Alves *et al* (1999) found a 19% difference (30% *v.* 11%) in remission rates favouring venlafaxine (75–150 mg/day) over fluoxetine (20–40 mg/day), which again was not statistically significant in a relatively small study (n=87).

Two studies reported inconsistent findings, with significant results favouring venlafaxine over fluoxetine using a global definition of remission but not according to the final HRSD score (see Table 4). Costa e Silva (1998) observed remission rates of 58% for venlafaxine (75–150 mg/day) and 35% for fluoxetine (20–40 mg/day) using a CGI numeric score of 1 to define remission, although 60% of the patients in each group remitted when an HRSD score of $\leqslant$7 was the criterion. Tzanakaki *et al* (2000) similarly found that the groups were comparable using an HRSD criterion ($<$7) but significantly different according to the CGI definition (see Table 4).

The three remaining studies found significant differences favouring venlafaxine; these studies all utilised maximum doses of $\geqslant$150 mg/day. Ballús *et al* (2000) observed remission rates of 59% for venlafaxine (75–150 mg/day) and 31% for paroxetine (20–40 mg/day). Mehtonen *et al* (2000), defining remission as a score of $<$10 on the 21-item version of the HRSD, reported rates of 68% for venlafaxine (75–150 mg/day) and 45% for sertraline (50–100 mg/day) among completers at week 8. Poirier & Boyer (1999) enrolled only patients who had failed to respond to at least two previous trials of antidepressants. About 75% had not responded to a prior course of SSRI therapy. They found a 19% advantage (37% *v.* 18%) in remission rates in favour of venlafaxine (200–300 mg/day) relative to paroxetine (20–40 mg/day).

Although these studies used various durations of treatment and definitions of remission, two conclusions are evident. First, there is no evidence that venlafaxine is more effective than the SSRIs at minimum therapeutic doses. Second, among the studies that permitted a venlafaxine dosage of $\geqslant$150 mg/day, there was a 14.4% average difference (range 5–23%) in remission rates favouring venlafaxine. It appears that the results of our pooled analysis would not have changed if we could have included these studies.

Other limitations

The generalisability of the results of a group of controlled clinical trials, like those of the individual studies, is limited by the exclusion of patients with more complex conditions, such as significant psychiatric and medical comorbidities. Although this lessens the relevance of these results to clinical practice, there is no reason to suspect that this exclusivity favours venlafaxine over the SSRIs. Other potential shortcomings of pooled analyses include problems with the reliability of dependent measures and the possibility that the results may be influenced by the data from one or two particularly large studies. We found significant differences between SSRIs and placebo, however, which indicates that the 'assay sensitivity' (Leber, 1991) of the pooled analysis was, at the least, sufficient to overcome measurement error. We also confirmed that the differences were not attributable to any particular study and extended across multiple definitions of remission.

Three more specific limitations can be considered. First, the SSRIs were lumped together as a class. Although there is no evidence that any SSRI is more effective than another, they are not truly interchangeable and some patients respond poorly to one SSRI but well to another (Edwards & Anderson, 1999). In this respect, our pooled analysis included a disproportionate number of patients treated with fluoxetine. The studies listed in Table 4 provide a broader range of comparisons and, in aggregate, yielded similar results. Nevertheless, among the 17 comparative studies included in the pooled analysis or summarised in Table 4, there is only one study each utilising fluvoxamine or sertraline and, to date, there are no studies of citalopram.

Second, all of the studies were short term. It is possible that a longer treatment period could have resulted in comparable remission rates.

Third, none of the studies used in the pooled analysis excluded patients who had failed to respond to other SSRIs. Because several SSRIs were already widely available when these studies were conducted, it is possible that the advantage observed for venlafaxine was delimited to a subgroup of patients who had previously failed trials of other SSRIs (see, for example, Poirier & Boyer, 1999).

CLINICAL IMPLICATIONS

- Patients treated with venlafaxine had a 10% greater chance of remission than those treated with SSRIs (45% *v.* 35%).
- Onset of remission occurred 1–2 weeks earlier for venlafaxine-treated patients.
- Doses of ⩾150 mg/day venlafaxine may be necessary to maximise the likelihood of remission.

LIMITATIONS

- Results of meta-analysis may be affected by the quality of the individual studies.
- Generalisability is limited by the exclusivity of clinical trial enrolment.
- There is not a sufficient number of studies to compare venlafaxine with specific SSRIs other than fluoxetine.

REFERENCES

Alves, C., for the Venlafaxine Study Group (1999) Efficacy and tolerability of venlafaxine and fluoxetine in outpatients with major depression. *Primary Care Psychiatry*, **5**, 57–63.

American Psychiatric Association (1987) *Diagnostic and Statistical Manual of Mental Disorders* (3rd edn, revised) (DSM–III–R). Washington, DC: APA.

—— (1993) Practice guideline for major depressive disorder in adults. *American Journal of Psychiatry*, **150** (suppl. 4), 1–26.

—— (1994) *Diagnostic and Statistical Manual of Mental Disorders* (4th edn) (DSM–IV). Washington, DC: APA.

Anderson, I. M. & Tomenson, B. M. (1994) The efficacy of selective serotonin re-uptake inhibitors in depression: a meta-analysis of studies against tricyclic antidepressants. *Journal of Psychopharmacology*, **8**, 238–249.

Ballús, C., Quiros, G., de Flores, T., et al (2000) The efficacy and tolerability of venlafaxine and paroxetine in outpatients with depressive disorder or dysthymia. *International Clinical Psychopharmacology*, **15**, 43–48.

Beasley, C. M., Jr., Dornseif, B. E., Bosomworth, J. C., et al (1991) Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. *British Medical Journal*, **303**, 685–692.

Breslow, N. E. & Day, N. E. (1980) *Statistical Methods in Cancer Research. Volume I. The Analysis of Case–Control Studies*. Lyons: IARC Scientific Publications.

Clerc, G. E., Ruimy, P., Verdeau-Paillès, J., et al (1994) A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for major depression and melancholia. *International Clinical Psychopharmacology*, **9**, 139–143.

Costa e Silva, J. (1998) Randomized, double-blind comparison of venlafaxine and fluoxetine in outpatients with major depression. *Journal of Clinical Psychiatry*, **59**, 352–357.

Depression Guideline Panel (1993) *Depression in Primary Care. Volume 2. Treatment of Major Depression*. Clinical Practice Guideline No. 5, AHCPR Publication No. 93-0551. Rockville, MD: US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research.

DeRubeis, R. J., Gelfand, L. A., Tang, T. Z., et al (1999) Medication versus cognitive behavior therapy for severely depressed outpatients: meta-analysis of four randomized comparisons. *American Journal of Psychiatry*, **156**, 1007–1013.

Diaz-Martinez, A., Benassini, O., Ontiveros, A., et al (1998) A randomized, open-label comparison of venlafaxine and fluoxetine in depressed outpatients. *Clinical Therapeutics*, **20**, 467–476.

Dierick, M., Ravizza, L., Realini, R., et al (1996) A double-blind comparison of venlafaxine and fluoxetine for treatment of major depression in outpatients. *Progress in Neuropsychopharmacology and Biological Psychiatry*, **20**, 57–71.

Duman, R. S., Heninger, G. R. & Nestler, E. J. (1997) A molecular and cellular theory of depression. *Archives of General Psychiatry*, **54**, 597–606.

Edwards, J. G. & Anderson, I. (1999) Systematic review and guide to selection of selective serotonin reuptake inhibitors. *Drugs*, **54**, 507–533.

Fava, G. A., Grandi, S., Zielezny, M., et al (1996) Four-year outcome for cognitive behavioral treatment of residual symptoms in major depression. *American Journal of Psychiatry*, **153**, 945–947.

Frank, E., Prien, R. F., Jarrett, R. B., et al (1991) Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. *Archives of General Psychiatry*, **48**, 851–855.

Hamilton, M. (1960) A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*, **23**, 56–62.

Harvey, A. T., Rudolph, R. L. & Preskorn, S. H. (2000) Evidence of the dual mechanisms of action of venlafaxine. *Archives of General Psychiatry*, **57**, 503–509.

Leber, P. (1991) Is there an alternative to the randomized controlled trial? *Psychopharmacology Bulletin*, **27**, 3–8.

McPartlin, G. M., Reynolds, A., Anderson, C., et al (1998) A comparison of once-daily venlafaxine XR and paroxetine in depressed outpatients treated in general practice. *Primary Care Psychiatry*, **4**, 127–132.

Mehtonen, O.-P., Behnke, K., Segaard, J., et al (2000) Randomized, double-blind comparison of venlafaxine and sertraline in outpatients with major depression. *Journal of Clinical Psychiatry*, **61**, 95–100.

Miller, I. W., Keitner, G. I., Schatzberg, A. F., et al (1998) The treatment of chronic depression. Part 3: psychosocial functioning before and after treatment with sertraline or imipramine. *Journal of Clinical Psychiatry*, **59**, 608–619.

Montgomery, S. A. & Åsberg, M. (1979) A new depression scale designed to be sensitive to change. *British Journal of Psychiatry*, **134**, 382–389.

Muth, E. A., Haskins, J. T., Moyer, J. A., et al (1986) Antidepressant biochemical profile of the novel bicyclic compound Wy-45,030, an ethyl cyclohexanol derivative. *Biochemical Pharmacology*, **35**, 4493–4497.

National Institute of Mental Health (1985) Clinical Global Impressions. *Psychopharmacology Bulletin*, **21**, 839–843.

Owens, M. J., Morgan, W. N., Plott, S. J., et al (1997) Neurotransmitter receptor transporter binding profile of antidepressants and their metabolites. *Journal of Pharmacology and Experimental Therapeutics*, **283**, 1305–1322.

Poirier, M.-F. & Boyer, P. (1999) Venlafaxine and paroxetine in treatment-resistant depression. Double-blind, randomised comparison. *British Journal of Psychiatry*, **175**, 12–16.

MICHAEL E. THASE, MD, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, Pittsburgh, PA. A. RICHARD ENTSUAH, PhD, RICHARD L. RUDOLPH, MD, Clinical Research and Development, Wyeth–Ayerst Research, Philadelphia, PA, USA

Correspondence: Michael E. Thase, Professor of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213-2593, USA

(First received 31 January 2000, final revision 10 August 2000, accepted 14 August 2000)

Prien, R. F., Carpenter, L. L. & Kupfer, D. J. (1991) The definition and operational criteria for treatment outcome of major depressive disorder: a review of the current research literature. *Archives of General Psychiatry*, **48**, 796–800.

Quitkin, F. M., Stewart, J. W., McGrath, P. J., et al (1993) Columbia atypical depression. A subgroup of depressives with better response to MAOI than to tricyclic antidepressants or placebo. *British Journal of Psychiatry*, **163** (suppl. 21), 30–34.

Redrobe, J. P., Bourin, M., Colombel, M. C., et al (1998) Dose-dependent noradrenergic and serotonergic properties of venlafaxine in animal models indicative of antidepressant activity. *Psychopharmacology*, **138**, 1–8.

Rothman, K. J. (1986) *Modern Epidemiology* Boston, MA: Little, Brown & Co.

Rudolph, R. L. & Feiger, A. D. (1999) A double-blind, randomized, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. *Journal of Affective Disorders*, **56**, 171–181.

—, Entsuah, R., Aguiar, L., et al (1998a) Early onset of antidepressant activity of venlafaxine compared with placebo and fluoxetine in outpatients in a double-blind study. *European Neuropsychopharmacology*, **8** (suppl. 2), S142.

—, Fabre, L. F., Feighner, J. P., et al (1998b) A randomized, placebo-controlled, dose–response trial of venlafaxine hydrochloride in the treatment of major depression. *Journal of Clinical Psychiatry*, **59**, 116–122.

Salinas, E., for the Venlafaxine XR 367 Study Group (1997) Once-daily extended release (XR) venlafaxine versus paroxetine in outpatients with major depression. *Biological Psychiatry*, **42** (suppl. 1), 244S.

Silverstone, P. H., Ravindran, A., for the Venlafaxine XR 360 Study Group (1999) Once-daily venlafaxine extended release (XR) compared with fluoxetine in outpatients with depression and anxiety. *Journal of Clinical Psychiatry*, **60**, 22–28.

Thase, M. E. (1998) Effects of venlafaxine on blood pressure: a meta-analysis of original data from 3744 depressed patients. *Journal of Clinical Psychiatry*, **59**, 502–508.

— (1999) How should efficacy be evaluated in randomized clinical trials of treatments for depression? *Journal of Clinical Psychiatry*, **60** (suppl. 4), 23–32.

—, Simons, A. D., McGeary, J., et al (1992) Relapse after cognitive behavior therapy of depression: potential implications for longer courses of treatment. *American Journal of Psychiatry*, **149**, 1046–1052.

—, Greenhouse, J. B., Frank, E., et al (1997) Treatment of major depression with psychotherapy or psychotherapy–pharmacotherapy combinations. *Archives of General Psychiatry*, **54**, 1009–1015.

Tylee, A., Beaumont, G., Bowden, M. W., et al (1997) A double-blind, randomized, 12-week comparison study of the safety and efficacy of venlafaxine and fluoxetine in moderate to severe major depression in general practice. *Primary Care Psychiatry*, **3**, 51–58.

Tzanakaki, M., Guazzelli, M., Nimatoudis, I., et al (2000) Increased remission rates with venlafaxine compared with fluoxetine in hospitalized patients with major depression and melancholia. *International Clinical Psychopharmacology*, **15**, 29–34.

Register or Login: Password:

Search This Periodical for

Advanced Search - MEDLINE - My Recent Sear

JOURNAL HOME
CURRENT ISSUE
BROWSE ALL ISSUES
ARTICLES IN PRESS
PRESS RELEASES
SEARCH THIS JOURNAL
JOURNAL INFORMATION
- Aims and Scope
- Editorial Board
- Editorial Disclosures
- Guide for Authors
- FAQs
- Info for Advertisers
- Abstracting/Indexing
- Contact Information
- Society Information
- Pricing Information

ONLINE SUBMISSIONS
SUBSCRIBE TO JOURNAL
RSS

1 Periodical Search Results

You searched within **Biological Psychiatry, Vol 52, Page 1166**

New Search | Edit Search | Save Search | Save Search as an E-mail Alert

Viewing 1-1 of 1 results **Results Page: [1]**

display checked docs | export citations | e-mail articles

Display: by Relevance, without preview, 20 per page

1. **Comparative efficacy between venlafaxine and SSRIs: a pooled analysis of patients with depression**
   Stephen M Stahl, Richard Entsuah, Richard L Rudolph
   Biological Psychiatry
   15 December 2002 (Vol. 52, Issue 12, Pages 1166-1174)
   Abstract | Full Text | Full-Text PDF (206 KB)

display checked docs | export citations | e-mail articles

Display: by Relevance, without preview, 20 per page

Viewing 1-1 of 1 results Results Page: [1]

New Search | Edit Search | Save Search | Save Search as an E-mail Alert

Behavioral Epigenetics Conference
October 29-30, 2010
Boston, MA
www.nyas.org/epi

More periodicals:
FIND A PERIODICAL
FIND A PORTAL
GO TO PRODUCT CATALOG

Copyright © 2010 Elsevier, Inc. All rights reserved | Privacy Policy | Terms & Conditions | Feedback | About Us | Help | Contact Us |
The content on this site is intended for health professionals.

Comparative Efficacy between Venlafaxine and SSRIs: A Pooled Analysis of Patients with Depression

Stephen M. Stahl, Richard Entsuah, and Richard L. Rudolph

Background: *Serotonergic and adrenergic enhancement may be synergistic and more effective than serotonergic enhancement alone in treating depression. The dual serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine is a dual reuptake inhibitor that may therefore offer greater efficacy than selective serotonin reuptake inhibitors (SSRIs).*

Methods: *Data from eight randomized, double-blind, controlled studies were pooled to compare efficacy in depressed patients receiving venlafaxine/venlafaxine extended release (XR), SSRIs, or placebo for ≤8 weeks. The mean changes from baseline in the 21-item Hamilton Rating Scale for Depression (HAM-D_{21}), Montgomery–Åsberg Depression Rating Scale (MADRS), and Clinical Global Impressions—Global Improvement (CGI-I) and CGI—Severity of Illness (CGI-S) item scores were compared, as were response rates derived from these scales.*

Results: *Statistically significant differences in mean HAM-D_{21} score decrease between venlafaxine (14.5) and SSRIs (12.6) and between the active treatments and placebo (11.3) were observed. Venlafaxine significantly decreased the mean MADRS scores more than SSRIs (17.8 vs. 15.9), and both treatments were significantly better than placebo (12.9). The same pattern of significance for CGI-I, HAM-D_{21}, and MADRS response rates between venlafaxine (71%, 64%, and 67%, respectively), SSRIs (64%, 57%, and 59%, respectively), and placebo (50%, 42%, and 41%, respectively) was observed.*

Conclusions: *Venlafaxine was significantly more effective than SSRIs in improving depression, perhaps due to enhancing both serotonin and norepinephrine.* Biol Psychiatry 2002;52:1166–1174 © *2002 Society of Biological Psychiatry*

Key Words: Norepinephrine, serotonin, depression, efficacy, venlafaxine, selective serotonin reuptake inhibitors

Introduction

Traditionally, all antidepressants are assumed to have comparable efficacy in clinical trials of depressed patients (American Psychiatric Association 2000; Depression Guideline Panel 1993). On the other hand, clinicians have recognized for decades that some patients respond better to one antidepressant than to another, and that combinations of drugs may be more effective than a single drug (Nelson et al 1991). This mismatch between clinical experience and clinical trials has been difficult to reconcile in part because clinical trials in the United States are often designed only to detect differences between an effective antidepressant and placebo, not to detect differences between two antidepressants (Prien 1994).

Recently, differences in antidepressant efficacy between two antidepressants have been demonstrated both prospectively, by increasing the power of the study with large sample sizes, and retrospectively, by pooling several studies in various meta-analyses (Anderson 1998, 2000; Anderson and Tomenson 1994; Ballús et al 2000; Costa e Silva 1998; Danish University Antidepressant Group 1986, 1990; Leinonen et al 1999; Mehtonen et al 2000; Poirier and Boyer 1999; Roose et al 1994; Stahl 2000; Tzanakaki et al 2000). This has led to a debate about whether the differences in antidepressant efficacy shown between two antidepressants in a clinical trial are due to differences in the drugs' mechanisms of therapeutic action, pharmacogenetic differences between patients who respond to one drug versus another, or differences in clinical trial design, such as dose selection for the different drugs. Although there is no consistent evidence of differences in efficacy between antidepressants with predominantly noradrenergic versus serotonergic actions (Nelson 1999), there is an emerging theme that agents with dual noradrenergic and serotonergic actions may be more efficacious than agents with selective serotonergic actions.

Although no study claims superior efficacy of a selective serotonin agent over a "dual-action" agent, numerous (Anderson 1998, 2000; Anderson and Tomenson, 1994; Thase et al 2001), but not all (Freemantle et al 2000), studies and meta-analyses show that "dual-action" tricyclic antidepressants, mirtazapine, milnacipran, venlafax-

From the Neuroscience Education Institute (SMS), Carlsbad, California; Wyeth Research (ARE, RLR), Philadelphia, Pennsylvania.
Address reprint requests to Stephen M. Stahl, M.D., Ph.D., Neuroscience Education Institute, 5857 Owens Avenue, Suite 102, Carlsbad CA 92009.
Received September 28, 2001; revised April 10, 2002; accepted April 12, 2002.

© 2002 Society of Biological Psychiatry

0006-3223/02/$22.00
PII S0006-3223(02)01425-7

BIOL PSYCHIATRY 2002;52:1166–1174

ine, and combinations of a serotonergic and noradrenergic agent have superior efficacy over single-action agents (Alves et al 1999; Ballús et al 2000; Costa e Silva 1998; Danish University Antidepressant Group 1986, 1990; Diaz-Martínez et al 1998; Leinonen et al 1999; Lopez-Ibor et al 1996; McPartlin et al 1998; Mehtonen et al 2000; Nelson et al 1991; Poirier and Boyer 1999; Roose et al 1994; Steffens et al 1997; Tylee et al 1997; Tzanakaki et al 2000). To test the hypothesis that dual-action agents have antidepressant efficacy superior to single-action agents, we analyzed a large sample of patients derived from pooling several studies of venlafaxine versus one or another of three selective serotonin reuptake inhibitors (SSRIs): fluoxetine, paroxetine, or fluvoxamine.

Methods and Materials

This evaluation was performed using pooled original data from patients who participated in eight clinical studies that directly compared venlafaxine and SSRIs. These studies were sponsored by the Clinical Research and Development Department at Wyeth Research during the development of the immediate-release (IR) and extended-release (XR) formulations of venlafaxine. The studies were all randomized, double-blind comparisons of the efficacy of venlafaxine and SSRIs in patients with major depression or major depressive disorder. Results from four of these studies have been published in their entirety (Clerc et al 1994; Dierick et al 1996; Rudolph and Feiger 1999; Silverstone et al 1999). Results from the fifth and sixth studies have been presented as posters and were published in abstract form (Rudolph et al 1998; Salinas et al 1998). The data from the remaining two studies have not yet been published (Studies 347 and 349; data on file, Wyeth Research, Philadelphia, PA). The studies were all comparable active-controlled evaluations of venlafaxine (75–375 mg/day) or venlafaxine XR (75–225 mg/day) versus fluoxetine (20–80 mg/day), paroxetine (20–40 mg/day), or fluvoxamine (100–200 mg/day) and were conducted in the United States, Europe, or Canada. Four of the eight studies also included placebo controls (Rudolph et al 1998; Rudolph and Feiger 1999; Salinas et al 1998; Silverstone et al 1999). Seven of the studies were outpatient trials; the eighth study (Clerc et al 1994) enrolled only inpatients. Each study was approved by the appropriate human ethics committees at the participating sites and was conducted according to the guidelines of the Declaration of Helsinki and its amendments. All patients provided explicit written informed consent. Table 1 summarizes the characteristics of each study included in the pooled analysis here.

Because one of the most important limitations of a pooled analysis is that the results can be biased by selection of a nonrepresentative group of studies, our data set included all completed trials conducted by Wyeth Pharmaceuticals; however, there are at least 12 other studies comparing venlafaxine and SSRIs for treatment of nonpsychotic depression, including three in which data analyses are not complete and another nine published studies for which we did not have access to the original data sets. These nine studies have been discussed extensively in a prior publication (Thase et al 2001) and based on that analysis, it appears that the results of our pooled analysis would not have changed if we could have included these studies.

Table 1. Overview of Studies Pooled for Meta-Analysis of Antidepressant Response

Study/author	Treatment groups	Daily dosage (mean)	Number of patients (ITT population)	Duration (weeks)
211/Rudolph and Feiger (1999)	Venlafaxine XR	75–225 mg (175 mg)	295	8
	Fluoxetine	20–60 mg (47 mg)		
	Placebo			
340/Clerc et al (1994)	Venlafaxine	100–200 mg (199 mg)	68	6
	Fluoxetine	20–40 mg (38 mg)		
347[a]	Venlafaxine	75–150 mg (129 mg)	111	6
	Fluvoxamine	100–200 mg (164 mg)		
348/Dierick et al (1996)	Venlafaxine	75–150 mg (112 mg)	302	8
	Fluoxetine	20 mg (20 mg)		
349[a]	Venlafaxine	75–150 mg (90 mg)	156	8
	Paroxetine	20–40 mg (24 mg)		
360/Silverstone et al (1999)	Venlafaxine XR	75–225 mg (141 mg)	357	12[b]
	Fluoxetine	20–60 mg (40 mg)		
	Placebo			
367/Salinas (1998)	Venlafaxine XR	75 mg (75 mg) 150 mg (150 mg)	324	8
	Paroxetine	20 mg (20 mg)		
	Placebo			
372/Rudolph et al (1998)	Venlafaxine	75–375 mg (240 mg)	459	6
	Fluoxetine	20–80 mg (54 mg)		
	Placebo			

ITT, intent to treat; XR, extended release.
[a]Unpublished data on file; Wyeth Research, Philadelphia, PA.
[b]For pooling, only results through week 8 were used.

Subjects

Patients could be enrolled in the studies if they were at least 18 years old and met the criteria of the DSM-III-R (American Psychiatric Association 1987) or DSM-IV (American Psychiatric Association 1994) for major depression or major depressive disorder, respectively, for at least 1 month before enrollment. Eligible patients were adult inpatients (n = 68) or outpatients (n = 1977) who had minimum scores (depending on the study) of either 20 on the 21-item Hamilton Rating Scale for Depression (HAM-D_{21}; Hamilton 1960) or 25 on the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg 1979) both prestudy and at baseline (study day –1), with no greater than a 20% decrease between the prestudy and baseline evaluation scores.

Patients with clinically significant cardiovascular disease, renal or hepatic disorders, seizure disorders, or a recent history of alcohol or drug abuse were excluded from study participation. Clinically significant abnormalities on the baseline physical examination, electrocardiogram (ECG), or laboratory tests were also reasons for exclusion from study participation. Patients who had known hypersensitivity to the study drugs and those who had used investigational or antipsychotic drugs within 30 days, a monoamine oxidase inhibitor within 14 days, or other antidepressant, anxiolytic, or sedative-hypnotic drugs within 7 days of the double-blind treatment period were also excluded. Patients who had taken any nonpsychopharmacologic drugs with psychotropic effects within 7 days of the double-blind treatment period were excluded unless a stable dosage of the drug had been maintained for at least a month before study start. The use of chloral hydrate (up to 2000 mg) was permitted at bedtime as a hypnotic in seven of the studies; the eighth study (Study 347, data on file, Wyeth Research, Philadelphia, PA) permitted the use of 20 mg temazepam at bedtime. Table 2 summarizes the sociodemographic and pretreatment clinical characteristics of the pooled study groups.

Study Drugs

Patients were randomly assigned to treatment with venlafaxine or venlafaxine XR (n = 865), an SSRI (fluoxetine, n = 563; paroxetine, n = 160; or fluvoxamine, n = 34), or placebo (four studies only, n = 450) during the double-blind treatment period at the daily dosages shown in Table 1. In some studies, the double-blind treatment phase was preceded by a single-blind placebo lead-in period of 7 ± 3 days.

Efficacy and Safety Assessments

The primary outcome measures were the HAM-D_{21} total score, the MADRS total score, and the Clinical Global Impressions Scale—Severity of Illness item (CGI-S; National Institute of Mental Health 1985) score. These were rated at baseline (study Day –1), before double-blind therapy, and along with the CGI—Global Improvement item (CGI-I) score on study days 7, 14, 21, 28, 42, and, for the 8-week studies, 56. Secondary outcome measures were the scores on the HAM-D_{21} depressed mood, agitation, anxiety-psychic, and anxiety-somatic items and the HAM-D_{21} anxiety/somatization, cognitive disturbance, and retardation factors.

Table 2. Baseline Characteristics of Intent-to-Treat Patient Population in the Pooled Studies

Characteristic	Venlafaxine (n = 851)	SSRIs (n = 748)	Placebo (n = 446)
Mean age (years)	42	42	41
Women (%)	65	64	62
Men (%)	35	36	38
Mean HAM-D_{21} total score	26	26	26
Mean MADRS total score	31	31	30
CGI-S score >4 (%)	53	53	36

SSRIs, selective serotonin reuptake inhibitors; HAM-D_{21}, 21-item Hamilton Rating Scale for Depression; MADRS, Montgomery-Åsberg Depression Rating Scale; CGI-S, Clinical Global Impressions scale-Severity of Illness item.

Safety and tolerability were evaluated based on reported adverse events throughout the study evaluation period and also on any changes that occurred in the physical examination, vital signs, 12-lead electrocardiogram recordings, and clinical laboratory tests during treatment. For the purposes of this report, only the common adverse events and the proportions of patients withdrawn from double-blind therapy due to adverse reactions were compared.

Statistical Analyses

Analyses were performed on data from intent-to-treat (ITT) patients; this ITT population included all patients who began the double-blind treatment phase, received at least one dose of study medication, and had at least one HAM-D_{21} evaluation during therapy or within 3 days of the last treatment day. The last-observation-carried-forward (LOCF) approach was used for missing observations and to include results from the 6-week studies in the week 8 efficacy assessment. Response was defined as a 50% or greater reduction from the baseline total scores for the HAM-D_{21} or MADRS totals. Patients who achieved a score of 1 or 2 on the CGI-I scale were considered responders as well.

Analysis of variance was used to assess the comparability of the three treatment groups (venlafaxine, SSRIs, or placebo) with respect to age and baseline HAM-D_{21} and MADRS total scores. Four separate analyses evaluating only HAM-D_{21} total scores were completed to corroborate results from the overall pooled analysis. They included 1) venlafaxine versus fluoxetine (only one venlafaxine study had a placebo arm, so a placebo comparison was excluded in this analysis), 2) venlafaxine XR versus fluoxetine and placebo (the majority [5/8] of the studies used fluoxetine as the SSRI comparator), 3) only placebo-controlled studies, and 4) only nonplacebo-controlled studies.

Baseline severity of depression was also assessed using the CGI-S. In addition, for both primary and secondary efficacy variables at each evaluation point, a two-way analysis of covariance of the mean change from baseline score was used, with baseline score as the covariate, and treatment and study type as factors. A multiple-comparisons technique, the protected Fisher F test, was applied at each evaluation point. Response rates were compared between treatment groups at each time point using Fisher's Exact Test.

All tests of hypotheses were two-sided. Results of statistical analyses were considered significant when p value was $\leq .05$.

Results

In total, 2117 patients were enrolled in the 8 trials; 2045 (97%) were included in the ITT analyses of the efficacy of venlafaxine and venlafaxine XR ($n = 851$), the SSRIs ($n = 748$), and placebo ($n = 446$). We excluded all data from 27 patients (at a single investigational site) before the analysis; the validity of the data could not be verified during the on-site monitoring review. Table 1 shows the average daily dose for each active treatment group in each of the eight trials. Within each trial, the average daily doses of the two active drugs were comparable based on a consideration of each drug's recommended dosage range.

Approximately two thirds of the patients were women. Baseline depression scores (Table 2) were similar for the three treatment groups, except significantly fewer patients randomized to placebo had CGI-S scores > 4 at baseline ($p < .001$) when compared with subjects randomized to receive venlafaxine or the SSRIs (36%, 53%, and 53%, respectively). Within the placebo-controlled studies, however, there were no differences between treatment groups in the baseline CGI-S scores.

Efficacy

HAM-D_{21} TOTAL. The adjusted mean changes from baseline scores at the final week (week 8) evaluation were –14.5, –12.6, and –11.3 for the respective groups (venlafaxine, SSRI, and placebo). Significant differences between venlafaxine and the SSRIs became apparent as early as week 2 of the double-blind phase and lasted through week 8 (Figure 1). Venlafaxine (IR and XR) was statistically significantly better than placebo at week 2 and all subsequent evaluation time points (Figure 1). The SSRIs were significantly superior to placebo at weeks 4 through 8. At week 8, venlafaxine produced a significantly higher response rate (64%) than the SSRIs (57%) and placebo (42%); the difference between the SSRIs and placebo in response rate was also statistically significant.

MADRS TOTAL. Similar trends were observed in the MADRS total scores (Figure 2). Adjusted mean changes from baseline scores at the week 8 evaluation were –17.8, –15.9, and –12.9 for venlafaxine, the SSRIs, and placebo, respectively. A statistically significant advantage for venlafaxine versus the SSRIs was observed starting at week 4 and continuing through week 8. Venlafaxine also had a statistically significant advantage over placebo from week 2 through week 8. The SSRIs were statistically significantly superior to placebo at week 2 and at week 4 through week 8. At week 8, venlafaxine produced a statistically

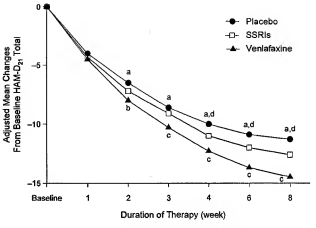

Figure 1. Last-observation-carried-forward analysis of 21-item Hamilton Rating Scale for Depression (HAM-D_{21}) changes from baseline over 8 weeks. $^{a}p < .001$, venlafaxine versus placebo; $^{b}p < .05$, venlafaxine versus selective serotonin reuptake inhibitors (SSRIs); $^{c}p \leq .001$, venlafaxine versus SSRIs; $^{d}p \leq .05$, SSRIs versus placebo.

significantly higher response rate (67%) than the SSRIs (59%) or placebo (41%), and the SSRIs were significantly better than placebo.

CGI-S. Statistically significant improvement was found for venlafaxine versus the SSRIs in the adjusted mean change from baseline scores on the CGI-S (Figure 3) beginning at week 2 and lasting throughout the 8-week evaluation period. Venlafaxine was also statistically significantly better than placebo from week 1 onward. The

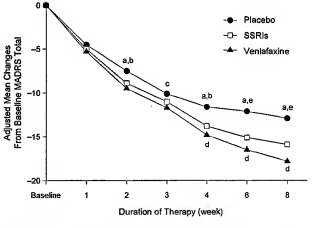

Figure 2. Last-observation-carried-forward analysis of Montgomery–Åsberg Depression Rating Scale (MADRS) total changes from baseline over 8 weeks. $^{a}p < .001$, venlafaxine versus placebo; $^{b}p < .05$, selective serotonin reuptake inhibitors (SSRIs) versus placebo; $^{c}p < .05$, venlafaxine versus placebo; $^{d}p \leq .05$, venlafaxine versus SSRIs; $^{e}p < .001$, SSRIs versus placebo.

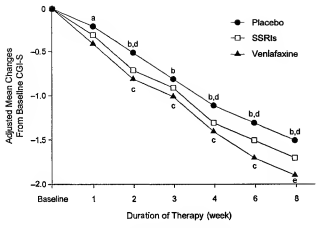

Figure 3. Last-observation-carried-forward analysis of Clinical Global Impressions Scale—Severity of Illness (CGI-S) changes from baseline over 8 weeks. $^{a}p < .05$, venlafaxine versus placebo, $^{b}p < .001$, venlafaxine versus placebo, $^{c}p < .05$, venlafaxine versus selective serotonin reuptake inhibitors (SSRIs), $^{d}p < .05$, SSRI versus placebo, $^{e}p = .001$, venlafaxine versus SSRIs.

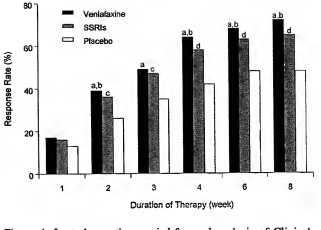

Figure 4. Last-observation-carried-forward analysis of Clinical Global Impressions Scale—Global Improvement (CGI-I) response rate over 8 weeks. $^{a}p \leq .001$, venlafaxine versus placebo; $^{b}p < .05$, venlafaxine versus selective serotonin reuptake inhibitors (SSRIs); $^{c}p < .05$, SSRIs versus placebo; $^{d}p \leq .001$, SSRIs versus placebo.

SSRIs had a statistically significant advantage over placebo at week 2 and at weeks 4 through 8.

CGI-I. At the week 8 evaluation, response rates were 71%, 64%, and 50% for the groups receiving venlafaxine, SSRIs, and placebo, respectively. Venlafaxine was statistically significantly better than the SSRIs and placebo beginning at week 2 and continuing through week 8, except at week 3, when the venlafaxine–SSRI difference did not reach statistical significance. The SSRIs also had a statistically significant advantage over placebo, beginning at week 2 and continuing through week 8 (Figure 4).

SECONDARY OUTCOME MEASURES. Statistically significant between-group differences were found for most of the secondary outcome measures at the final evaluation. The mean changes from baseline scores for venlafaxine exceeded those of the SSRIs for all secondary outcome measures (see Efficacy and Safety Assessments for a list). Similarly, venlafaxine demonstrated greater efficacy than placebo on all the secondary outcome measures, and the SSRIs were better than placebo on most of these measures as well.

Subset Analyses

VENLAFAXINE VERSUS FLUOXETINE. An analysis of covariance restricted to studies comparing venlafaxine and fluoxetine (Table 1) indicated that, based on the HAM-D_{21} total score ($n = 659$), venlafaxine was significantly better than fluoxetine from week 3 through week 8 (LOCF; Figure 5). There was a significant difference between venlafaxine and fluoxetine in the number of responders at week 8 (70% vs. 59%, respectively; $p = .003$).

VENLAFAXINE XR VERSUS FLUOXETINE VERSUS PLACEBO. An analysis of covariance restricted to studies comparing venlafaxine XR, fluoxetine, and placebo (Table 1) indicated that, based on the HAM-D_{21} total score ($n = 648$), venlafaxine XR was significantly better than placebo from week 2 through week 8. Fluoxetine showed similar trends over placebo, with the exception that the difference at week 3 was not statistically significant (LOCF; Figure 6). There was no significant difference between venlafaxine XR and fluoxetine in the number of responders at week 8, but the venlafaxine XR (59%)/

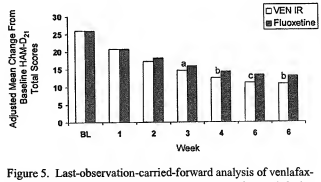

Figure 5. Last-observation-carried-forward analysis of venlafaxine (VEN) versus fluoxetine over 8 weeks. $^{a}p < .05$, venlafaxine versus fluoxetine; $^{b}p < .01$, venlafaxine versus fluoxetine; $^{c}p < .001$, venlafaxine versus fluoxetine. HAM-D_{21}, 21-item Hamilton Rating Scale for Depression.

BIOL PSYCHIATRY
2002;52:1166–1174

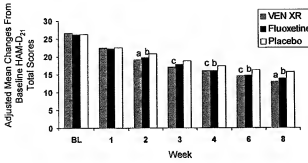

Figure 6. Last-observation-carried-forward analysis of venlafaxine extended release (VEN XR) versus fluoxetine versus placebo over 8 weeks. $^{a}p \leq .001$, venlafaxine XR versus placebo; $^{b}p \leq .05$, fluoxetine versus placebo; $^{c}p < .05$, venlafaxine XR versus placebo. HAM-D_{21}, 21-item Hamilton Rating Scale for Depression.

placebo (41%) and fluoxetine (54%)/placebo comparisons were significant ($p < .001$ and $p = .007$, respectively).

PLACEBO-CONTROLLED STUDIES. An analysis of covariance restricted to studies with a placebo arm (Table 1) indicated that, based on the HAM-D_{21} total score ($n = 1410$), venlafaxine/venlafaxine XR was significantly better than the SSRIs and placebo from week 2 through week 8. The SSRIs were significantly better than placebo at week 4 through week 8 (LOCF; Figure 7). There was no significant difference between venlafaxine XR and fluoxetine in the number of responders at week 8, but the venlafaxine XR/placebo and fluoxetine/placebo comparisons were significant ($p < .001$ and $p = .007$, respectively).

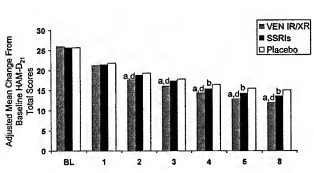

Figure 7. Last-observation-carried-forward analysis of venlafaxine and venlafaxine extended release (VEN/VEN XR) versus selective serotonin reuptake inhibitors (SSRIs) versus placebo (placebo-controlled) over 8 weeks. $^{a}p < .001$, VEN/VEN XR versus placebo; $^{b}p < .05$, SSRIs versus placebo; $^{c}p < .05$, VEN/VEN XR versus placebo; $^{d}p < .001$, VEN/VEN XR versus SSRIs. HAM-D_{21}, 21-item Hamilton Rating Scale for Depression.

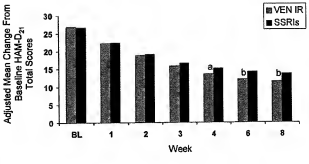

Figure 8. Last-observation-carried-forward analysis of venlafaxine (VEN) versus selective serotonin reuptake inhibitors (SSRIs; nonplacebo-controlled) over 8 weeks. $^{a}p < .05$, venlafaxine IR versus SSRIs; $^{b}p < .01$, venlafaxine versus SSRIs. HAM-D_{21}, 21-item Hamilton Rating Scale for Depression.

NONPLACEBO-CONTROLLED STUDIES (ALL VENLAFAXINE STUDIES). An analysis of covariance restricted to studies comparing venlafaxine and fluoxetine (Table 1) indicated that, based on the HAM-D_{21} total score ($n = 635$), venlafaxine was significantly better than fluoxetine from week 4 through week 8 (LOCF; Figure 8). There was no significant difference between venlafaxine and fluoxetine in the number of responders at week 8.

Safety

Table 3 shows the most commonly reported treatment-emergent adverse events for the pooled sample. The most commonly recorded adverse event for all treatment groups was nausea.

Of the venlafaxine-treated patients, 9% discontinued treatment because of adverse reactions, compared with 7% of the SSRI-treated patients and 2% of the placebo-treated patients (Fisher's Exact Test; $p = .001$, venlafaxine vs. placebo and SSRI vs. placebo; venlafaxine vs. SSRI comparison was not significant, $p = .185$).

Table 3. Percentages of Treatment-Emergent Adverse Events Among All Patients (Pooled Studies, $n = 2117$)

Study Event	Venlafaxine ($n = 895$)	SSRIs ($n = 769$)	Placebo ($n = 453$)
Nausea	24	18	16
Dizziness	13	7	9
Insomnia	11	10	11
Dry Mouth	12	8	10
Somnolence	5	7	5
Constipation	9	4	9
Sweating	10	8	5
Nervousness	5	5	4
Tremor	4	11	1
Pharyngitis	5	5	10

SSRIs, selective serotonin reuptake inhibitors.

Discussion

Our analysis of a large pooled sample of depressed patients treated with venlafaxine, an SSRI, or placebo showed that the "dual-action" serotonergic–noradrenergic agent venlafaxine had greater efficacy than the "single-action" SSRIs. This finding stands in contrast to the widely held assumption that all antidepressants are equally effective. The randomized clinical trials that have supported this assumption have not been adequately powered to detect differences between two antidepressants, however, because these differences would be smaller than those generally observed between an antidepressant and placebo. For instance, when presented individually, each of the eight studies pooled here had less than 40% power to detect a difference between an SSRI and venlafaxine; some had as little as 7% power. Thus, it is not surprising that studies with sample sizes of less than 300 patients per treatment group (the size necessary for 80% power to detect the differences observed here) have failed to detect differences between dual-action versus single-action antidepressants.

In this pooled analysis, the differences between venlafaxine and the SSRIs were observed as early as week 2. At the final week of assessment (week 8), venlafaxine produced significantly greater improvement than did the SSRIs on the adjusted mean change from baseline score on each of the primary outcome measures, which included the HAM-D_{21} total score, the MADRS total score, and the CGI-S score. Similarly, CGI-I response rates favored venlafaxine over the SSRIs beginning at week 2 and persisting through week 8. The differences in response rates between venlafaxine (71%) and the SSRIs (64%) at week 8 were found to be statistically significant. The power to detect this effect size was 80%.

Results from the additional selective analyses including smaller-sized groups were consistent with the trends shown in the overall pooled analysis with one exception. The venlafaxine XR versus fluoxetine versus placebo comparison revealed no appreciable differences between venlafaxine XR and fluoxetine at any observation point, but significant differences were observed between venlafaxine and fluoxetine beginning at week 3. This outcome is in line with the failure by Freemantle and colleagues (Freemantle et al 2000) to detect significant differences in their meta-regression analysis of SSRIs and alternative antidepressants using a sample size of 105, compared with Thase et al (2001), who determined in a meta-analysis a significant difference between venlafaxine and SSRIs based on a sample size of 2045.

There are a number of limitations of the use of data obtained from this pooled analysis, including combining studies of different dosing schedules, especially relevant for venlafaxine because its dual action appears to be dose dependent. Another limitation is the drawing of broad conclusions about SSRIs when most of the studies used the same SSRI. These limitations have been discussed at length in a recent publication based on these same pooled data, which found higher remission rates for venlafaxine over the SSRIs (Thase et al 2001).

Our findings showing higher response rates and greater changes in clinical ratings of depression for venlafaxine in comparison to SSRIs on the HAM-D_{21}, MADRS, and CGI extend the findings of Thase et al; however, because of the short-term nature of the studies included in this analysis, it is unclear whether SSRIs may exhibit comparable efficacy to venlafaxine when treatment exceeds 8 weeks or whether venlafaxine will maintain its therapeutic advantage over SSRIs during continuation-phase treatment. Nonetheless, our data at least suggest that venlafaxine has a faster onset of action compared with SSRIs.

Our findings are also consistent with several but not all reports and meta-analyses showing superior efficacy for a number of dual-action agents, including tricyclic antidepressants, mirtazapine, milnacipran, and the combination of a serotonergic and a noradrenergic agent (Alves et al 1999; Anderson and Tomenson 1994; Ballús et al 2000; Costa e Silva 1998; Danish University Antidepressant Group 1986, 1990; Diaz-Martinez et al 1998; Leinonen et al 1999; Lopez-Ibor et al 1996; McPartlin et al 1998; Mehtonen et al 2000; Nelson et al 1991; Poirier and Boyer 1999; Roose et al 1994; Steffens et al 1997; Tylee et al 1997; Tzanakaki et al 2000). Although venlafaxine is classified as a dual-action agent in the data reported in these studies as well as those presented here, it should be pointed out that an analysis of platelet serotonin reuptake and pressor response to tyramine using venlafaxine indicated that this dual-action agent inhibited serotonin reuptake at low doses and inhibited both serotonin and norepinephrine reuptake at high doses (i.e., pressor response to tyramine was appreciably blunted at high doses and not at 75 mg/day; Harvey et al 2000). Ultimately, therefore, the possibility that dual-action agents have greater antidepressant efficacy than single-action agents will need to be explored in large prospective trials and at various doses. In selecting an antidepressant for an individual patient, one must also bear in mind not only the efficacy of the various treatment options available, but also the clinical relevance of adverse event and safety profiles, drug interactions, emerging pharmacogenomic factors, and factors related to subpopulations of depression.

Preparation of this manuscript was supported by an unrestricted educational grant from Wyeth Research, Philadelphia, Pennsylvania. Dr. Stahl, consultant to Wyeth Laboratories and a member of their speakers'

bureau, has received research grants from Wyeth Laboratories. He has also received research grants from the manufacturers of fluoxetine (Dista Products, Indianapolis, IN), sertraline (Pfizer, New York, NY), paroxetine (GlaxoSmithKline Pharmaceuticals, Research Triangle Park, NC), citalopram (Forest Pharmaceuticals, St Louis, MO), and fluvoxamine (Solvay Pharmaceuticals, Marietta, GA). Dr. Rudolph is a former employee of Wyeth Research, and is currently an employee of Cyberonics, Houston, Texas.

References

Alves C, Cachola I, Brandao J (1999): Efficacy and tolerability of venlafaxine and fluoxetine in outpatients with major depression. *Primary Care Psychiatry* 5:57–63.

American Psychiatric Association (1987): *Diagnostic and Statistical Manual of Mental Disorders: DSM-III-R*, 3rd ed. Washington, DC: American Psychiatric Association.

American Psychiatric Association (1994): *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*, 4th ed. Washington, DC: American Psychiatric Association.

American Psychiatric Association (2000): Practice guideline for the treatment of patients with major depressive disorder (revision). *Am J Psychiatry* 157(suppl):1–45.

Anderson IM (1998): SSRIs versus tricyclic antidepressants in depressed inpatients: A meta-analysis of efficacy and tolerability. *Depress Anxiety* 7(suppl 1):11–17.

Anderson IM (2000): Selective serotonin reuptake inhibitors versus tricyclic antidepressants: A meta-analysis of efficacy and tolerability. *J Affect Disord* 58:19–36.

Anderson IM, Tomenson BM (1994): The efficacy of selective serotonin re-uptake inhibitors in depression: A meta-analysis of studies against tricyclic antidepressants. *J Psychopharmacol* 8:238–249.

Ballús C, Quiros G, de Flores T, de la Torre J, Palao D, Rojo L, et al (2000): The efficacy and tolerability of venlafaxine and paroxetine in outpatients with depressive disorder or dysthymia. *Int Clin Psychopharmacol* 15:43–48.

Clerc GE, Ruimy P, Verdeau-Paillès J, on behalf of the Venlafaxine French Inpatient Study Group (1994): A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for major depression and melancholia. *Int Clin Psychopharmacol* 9:139–143.

Costa e Silva J (1998): Randomized, double-blind comparison of venlafaxine and fluoxetine in outpatients with major depression. *J Clin Psychiatry* 59:352–357.

Danish University Antidepressant Group (1986): Citalopram: Clinical effect profile in comparison with clomipramine: A controlled multicenter study. *Psychopharmacology* 90:131–138.

Danish University Antidepressant Group (1990): Paroxetine: A selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. *J Affect Disord* 18:289–299.

Depression Guideline Panel. (1993, April): Clinical Practice Guideline Number 5: Depression in Primary Care. Vol. 1: Detection and Diagnosis AHCPR Publication 93–0550. Rockville, MD: U.S. Dept of Health and Human Services, Agency for Health Care Policy and Research.

Diaz-Martinez A, Benassinni O, Ontiveros A, Gonzalez S, Salin R, Basquedano G, et al (1998): A randomized, open-label comparison of venlafaxine and fluoxetine in depressed outpatients. *Clin Ther* 20:467–476.

Dieriek M, Ravizza L, Realini R, Martin A (1996): A double-blind comparison of venlafaxine and fluoxetine for treatment of major depression in outpatients. *Prog Neuropsychopharmacol Biol Psychiatry* 20:57–71.

Freemantle N, Anderson IM, Young P (2000): Predictive value of pharmacological activity for the relative efficacy of antidepressant drugs: Meta-regression analysis. *Br J Psychiatry* 177:292–302.

Hamilton M (1960): A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23:56–62.

Harvey AT, Rudolph RL, Preskorn SH (2000): Evidence of the dual mechanisms of action of venlafaxine. *Arch Gen Psychiatry* 57:503–509.

Leinonen E, Skarstein J, Behnke K, Agren H, Helsdingen JT, and the Nordic Antidepressant Study Group (1999): Efficacy and tolerability of mirtazapine versus citalopram: A double-blind, randomized study in patients with major depressive disorder. *Int Clin Psychopharmacol* 14:329–337.

Lopez-Ibor J, Guelfi JD, Pletan Y, Tournoux A, Prost JF (1996): Milnacipran and selective serotonin reuptake inhibitors in major depression. *Int Clin Psychopharmacol* 11(suppl 4):41–46.

McPartlin GM, Reynolds A, Anderson C, Casoy J (1998): A comparison of once-daily venlafaxine XR and paroxetine in depressed outpatients treated in general practice. *Primary Care Psychiatry* 4:127–132.

Mehtonen O-P, Søgaard J, Roponen P, Behnke K, for the Venlafaxine 631 Study Group (2000): Randomized, double-blind comparison of venlafaxine and sertraline in outpatients with major depressive disorder. *J Clin Psychiatry* 61:95–100.

Montgomery SA, Åsberg M (1979): A new depression scale designed to be sensitive to change. *Br J Psychiatry* 134:382–389.

National Institute of Mental Health (1985): Clinical Global Impressions. *Psychopharmacol Bull* 21:839–843.

Nelson JC (1999): A review of the efficacy of serotonergic and noradrenergic reuptake inhibitors for treatment of major depression. *Biol Psychiatry* 46:1301–1308.

Nelson JC, Mazure CM, Bowers MB Jr, Jatlow PI (1991): A preliminary, open study of the combination of fluoxetine and desipramine for rapid treatment of major depression. *Arch Gen Psychiatry* 48:303–307.

Poirier M-F, Boyer P (1999): Venlafaxine and paroxetine in treatment-resistant depression: Double-blind, randomised comparison. *Br J Psychiatry* 175:12–16.

Prien RF (1994): *Clinical Evaluation of Psychotropic Drugs: Principles and Guidelines*. New York: Lippincott Williams and Wilkins.

Roose SP, Glassman AH, Attia E, Woodring S (1994): Comparative efficacy of selective serotonin reuptake inhibitors and tricyclics in the treatment of melancholia. *Am J Psychiatry* 151:1735–1739.

Rudolph R, Entsuah R, Aguiar L, Derivan A (1998, November): Early onset of antidepressant activity of venlafaxine compared with placebo and fluoxetine in outpatients in a double-

blind study. Poster presented at the Annual Meeting of the European College of Neuropsychopharmacology, Paris, France.

Rudolph RL, Feiger AD (1999): A double-blind, randomized, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. *J Affect Disord* 56:171–181.

Salinas E, for the Venlafaxine 367 Study Group (1998, November): Once-daily venlafaxine XR versus paroxetine in outpatients with major depression. Poster presented at the Annual Meeting of the European College of Neuropsychopharmacology, Paris, France.

Silverstone PH, Ravindran A, for the Venlafaxine XR 360 Study Group (1999): Once-daily venlafaxine extended release (XR) compared with fluoxetine in outpatients with depression and anxiety. *J Clin Psychiatry* 60:22–28.

Stahl SM (2000): Placebo-controlled comparison of the selective serotonin reuptake inhibitors citalopram and sertraline. *Biol Psychiatry* 48:894–901.

Steffens DC, Krishnan KRR, Helms MJ (1997): Are SSRIs better than TCAs? Comparison of SSRIs and TCAs: A meta-analysis. *Depress Anxiety* 6:10–18.

Thase ME, Entsuah AR, Rudolph RL (2001): Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry* 178:234–241.

Tylee A, Beaumont G, Bowden MW, Reynolds A, on behalf of the General Practice Study Group (1997): A double-blind, randomized, 12-week comparison study of the safety and efficacy of venlafaxine and fluoxetine in moderate to severe major depression in general practice. *Primary Care Psychiatry* 3:51–58.

Tzanakaki M, Guazzelli M, Nimatoudis I, Zissis NP, Smeraldi E, Rizzo F (2000): Increased remission rates with venlafaxine compared with fluoxetine in hospitalized patients with major depression and melancholia [erratum published *Int Clin Psychopharmacol* 2001;15:120]. *Int Clin Psychopharmacol* 15:29–34.